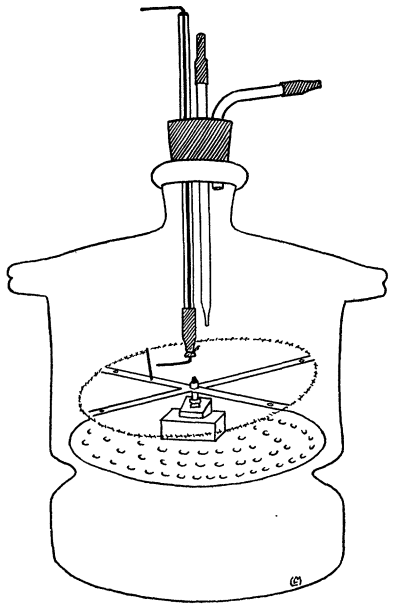
A DEMONSTRATION JAR FOR WHITE MICE

A MOUSE in a closed vessel of known capacity is a favored way of showing roughly some of the effects of inhalation anesthetics. Motor excitement and depression may be noted, but not well, for in the limited space the mouse has nowhere to run. For this reason we have mounted a simple tread-mill in a 5 liter desiccator, so arranged that the number of revolutions is recorded on a slow kymograph. The apparatus is easily constructed without expense and permits a number of interesting experiments and demonstrations.

The wheel is a circle of screen wire just smaller than the inner diameter of the desiccator, thumbtacked to two light pieces of wood at right angles to each other. Its bearing is a piece of glass tubing about 2 cm long pushed through a tight hole where the sticks cross. The ends of the tubing are fused down until they fit freely, but without unnecessary play, a small finishing nail. With a washer below this makes a very freely turning wheel, and when mounted on a block at about 30° to the horizontal the mouse has no trouble and apparently a good deal of pleasure in running it.

The recording device is very simple. A piece of glass tubing about 18 cm long is put through a hole in a rubber stopper in the top of the desiccator. The ends of this tube are fused down to fit loosely a piece of iron wire. A short piece of rubber tubing is fitted over the lower end of the glass tube and tied securely around the wire. This makes a gas-tight joint, and also serves as a spring to resist rotation of the wire. Each end of the wire is bent at right angles. The lower bend is hit by a pin on the revolving wheel, the upper end is connected by a thread to a damped-down muscle lever. Thus every revolution of the mouse wheel, in either direction, is made to record on



the kymograph, which of course also carries a suitable time tracing. Two other glass tubes through the rubber stopper allow gas or volatile liquids to be run in. An electrical contact is avoided in the recording mechanism because of the explosibility of several of the anesthetic mixtures.

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SPECIAL ARTICLES

VARIABILITY AND INDIVIDUALITY

IN 1920 the writer[1] published data which demonstrated that young animals of an inbred strain of mice showed a significantly higher percentage of growth of an inoculated tumor than did sexually mature individuals of the same strain. Strong[2] confirmed these results with different material and showed in addition that senile animals resembled very young animals in that they exhibited an increased tolerance of tumor implants as compared with that of young adults. These data were interpreted as indicating that the full expression of the genetic constitution of the individual was being assumed gradually during the period of infancy and adolescence, reached its most characteristic manifestation at the young adult stage and became less integrated and more decentralized during senility.

Warthin,[3] Child[4] and others have considered senility as a period of *involution*, and have looked upon individuality as a process directly measurable by the degree of manifestation of certain functions.

From evidence derived from a considerable mass of material it would appear that variability of a function or characteristic is a more fundamental indication of the nature of individuality than is the mean value of any physiological or morphological characteristic at any given time.

When, for example, variables of a genetic nature are reduced to a minimum for mammalian material by the use of closely inbred strains and when the

[1] *Jour. Exper. Zool.*, 31: 307–326, 1920.
[2] *Jour. Exper. Zool.*, 36: 67–134, 1922.
[3] "Old Age The Major Involution," Hoeber, N. Y., 1929.
[4] "Senescence and Rejuvenescence," Univ. of Chicago Press, 1915.

ontogenetic variables are to some extent controlled by the use of one sex and by the choice of some physiological function confined to a restricted period of the life cycle, the experimental conditions are simplified to a considerable degree.

Data derived from females of an inbred strain of mice (dbr) under investigation by Dr. W. S. Murray are available to show variation in litter size at various ages of the mother. When the coefficient of variation of litter size at successive 30-day periods of maternal age is calculated the following results are obtained.

Age of mother in days	No. of litters	Mean litter size	Coefficient of variation
– 75	517	4.189	42.46
76–105	1298	4.985	38.81
106–135	1026	5.436	36.94
136–165	978	5.598	36.96
166–195	762	5.767	35.43
196–225	691	5.363	40.25
226–255	598	5.055	40.60
256–285	433	5.173	41.52
286–315	286	5.108	43.45
316–345	194	4.613	51.94
346–375	105	4.314	47.46
376–405	49	4.469	41.70
406–	34	3.470	58.56

It will be noted that variation in litter size begins high, decreases, reaches a base level and then increases again as reproductive activity decreases and senility sets in.

A very similar result with, however, a shorter constant base level period was obtained for another inbred strain of mice (C 57). The slight difference between the two strains is probably a natural concomitant of the genetic characteristics which they each possess.

Looked at from the point of view of variation in physiological response to a constant stimulus, the work of the writer and of Strong on inoculated tumors already referred to, agrees in general with the data on litter size. In so far as somatic tissues are concerned there is good reason to believe that the age-variability relationship above described may be of general applicability.

The next question is whether a similar relative change in variability incidental to age applies also to the functioning of the germ cell. On *a priori* grounds there is no reason why the germ cell, as an organization, should not also show a durational phase in its various activities.

Data presented by Bridges[5] bear on this point. Using "crossing-over" between genes as an index and *Drosophila* as material he studied the relation of age to the absolute amount of crossing-over. He did not, however, analyze his data from the point of view of *variability* of the function of crossing-over in relation to the age of the mother. When his data for single cross-overs are studied with this point in mind certain suggestive and interesting results are obtained.

The average variability in his two main tables shows the following distribution according to the age of the mother.

Age period of mother from youngest to oldest	Percentage of variability in single "crossing-over"
1	39.52
2	30.17
3	18.83
4	22.82
5	24.00
6	21.96
7	14.63
8	12.56
9	4.87
10	15.27
11	26.53
12	34.82

Again the very young and the very old females show the most variation. There is a secondary decrease in the third period but the primary stability seems to be in the ninth. While the evidence is not conclusive it supports the idea that very young and very old germ cells function more variably than do those of the middle-age periods.

This is an important conclusion and if substantiated by further data on different materials will lead us far towards a better understanding of various general evolutionary problems of prime importance.

(1) It might well develop that tendency to mutation, which in itself is an indication of variability, would be greater in very young and in very old germ cells.

(2) If this were true, domestication, in which very young and very old animals, protected from the competitive factor of natural selection, are used as parents, would provide a far greater chance for mutations to occur than would natural conditions.

(3) Similarly, somatic mutations would tend to be more frequent in very young or very old animals. Evidence that this is the case is to be found in the work of Strong,[6] Bittner[7, 8] and Cloudman,[9] who found genetic differences in spontaneous mammary

[5] Carnegie Inst. of Wash., Publ. No. 399, 1929.

[6] *Jour. Cancer Research*, 13: 103–115, 1926.
[7] *Am. Jour. Cancer*, 15: 2202–2247, 1931.
[8] *Am. Jour. Cancer*, in press.
[9] *Am. Jour. Cancer*, 16: 568–630, 1932.

neoplasms produced by a single individual mouse. These various animals had very evidently reached a point where central physiological control of the variability of somatic cell variation had diminished to a stage where they no longer acted as individuals in the restricted sense.

(4) The origin of neoplasms as the result of the fundamental disintegration of a centrally controlled "individuality" would become more clearly established. Different types of neoplasms would naturally be expected to follow different age distributions—as they do—because the different tissues are organ systems of the body "age" physiologically at very different periods in ontogeny. As matters stand there seems to be sufficient evidence to conclude:

(1) "Individuality" in mammals and probably in all higher animals is a relative term with a well-pronounced durational phase.

(2) Within genetically comparable material, variability in form and function is greater in the very young and in the very old than it is in the height of reproductive efficiency.

(3) Measurements of simple increase or decrease in function are not sufficient to give a complete picture of the nature of individuality.

(4) Senility is not simply a "major involution" but rather a period at which the disintegration of individuality is the most interesting biological phenomenon. "Involution" as a concept suggests the opposite of "evolution." It would be much more accurate to consider old age as a period primarily of a type of physiological and morphological disintegration and incoordination.

(5) All studies of genetic characters in animals should consider the age factor as an important variable likely to influence fundamentally the justifiable conclusions as to the type and nature of the character under consideration.

(6) This applies not only to genetic characters and processes outside of the germ-plasm but to such characters and processes as mutation, crossing-over, and other chromosomal aberrations. It may be expected that variability in relation to age will be operative in all germ cells to a more nearly comparable degree than it will be in the somatic characters of various groups of organisms.

(7) There is, however, little likelihood of general mathematical values for such variation being immediately established since the genetic characters of strains and individuals would be expected to vary in so far as they affect the assumption and degeneration of "individuality."

(8) The existence of the durational phase in the development of individuality helps to bridge the gap which has existed between physiologic and theoretic genetics. It shows that geneticists must recognize and consider that factor before the gene-character relationship can become sufficiently definite to allow accurate evaluation of gene location, dominance and other genetic phenomena.

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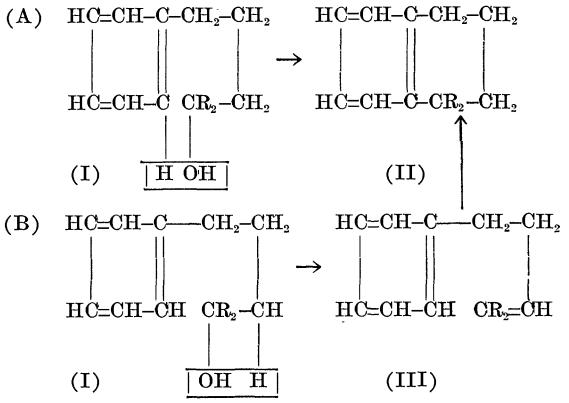
THE MECHANISM OF THE IONENE SYNTHESIS

IN a recent report[1] we described a synthesis of ionene that for the first time provides convincing evidence of the constitution of this interesting hydrocarbon, which has so lately risen to prominence in connection with studies of the structure of vitamin A.

Further work by Davidson and Apfelbaum, in these laboratories, has now thrown additional light upon the mechanism of this synthesis, in so far as the transition from a monocyclic tertiary alcohol (I) to a dicyclic hydrocarbon of ionene type (II) is concerned.

Manifestly, such a cyclization involves the elimination of a molecule of water, and this may be accomplished by the OH of the tertiary alcohol removing an H, either from the benzene nucleus, thus forming the second cycle, as shown in (A); or (B), from the adjacent CH_2 group, with production of the olefin (III), which then isomerizes to the dicyclic hydrocarbon (II), a type of rearrangement not at all uncommon in terpene chemistry:



Since the next lower homolog (I) is much more easily prepared than the tertiary alcohol used for the synthesis of ionene itself, this was used in our experiments, as shown in the formulas above, and gave the corresponding lower homolog (II) of ionene.

That (B), rather than (A), represents what actually occurs in this cyclization is indicated by the following experimental facts:

[1] M. T. Bogert, SCIENCE, n.s., 76: 1977, 475, November 18, 1932.