ON THE EFFECT OF CONTINUED ADMINISTRATION OF CERTAIN POISONS TO THE DOMESTIC FOWL, WITH SPECIAL REFERENCE TO THE PROGENY.[1]

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I. The Problem.

(Read April 15, 1916.)

One of the outstanding problems of genetics is that of the origin of new heritable variations. With the passage of time and the accumulation of exact experimental data it becomes increasingly clear that this factor is the basic one in all evolutionary change, whether progressive or retrogressive. Just now it is the fashion to speak of new heritable variations as mutations, but such designation does not appear either to make the facts concerned any different from what they were under an older terminology, nor does it essentially contribute to our knowledge about them. Indeed it is, so far as I can see, entirely fair to say that but little in the way of essential advance has been towards the solution of this problem since Darwin's examination and analysis of it. The two leading students of variation since Darwin, Bateson and De Vries, have to be sure, contributed greatly to our knowledge of certain aspects of the phenomena of variation; notably, on the one hand, in the direction of establishing a number of definite principles or laws of morphogenesis which control or determine in large degree the somatic expression of germinal differences, and, on the other hand, in very precisely and minutely analyzing the genetic behavior of various heritable variations, after they have appeared. But it is the problem of the origin, the determination, the causes of those *germinal* differences which lie behind somatic variations, and indeed *are* the

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heritable variations, which appears to be the basic problem of genetics.

One may expose systematically the germ-cells of an animal to something unusual or abnormal in the surrounding conditions, and then analyze, so far as may be, not only the new heritable variations themselves (provided any such appear), but also the factors which underlie their causation. One is the more encouraged to undertake experimentation in this direction, because of the very interesting results of such studies which have been reported during the last few years, particularly those of Stockard[2] and Cole,[3] with mammals and birds. In this connection mention should also be made of the work of Sumner with mice, Kammerer with lower vertebrates, Tower with insects, and MacDougal with plants.

The problems with which this investigation deals are specifically these:

1. Does the continued administration of ethyl alcohol (or similar narcotic poisons) to the domestic fowl induce precise and specific changes in the germinal material, such as to lead to new, heritable, somatic variations?

2. Failing a specific effect is there a general effect upon the germinal material leading to general degeneracy of the progeny?

3. What in general are the effects upon the soma of the treated individual of the continued administration of such poisons?

4. Are the somatic effects upon the treated individuals of a sort to give any clue as to the probable origin, or mechanism of the germinal changes?

The present paper reports, in brief abstract, the results obtained from the beginning of the experiment in September, 1914, to February 1, 1916. A complete report is now in process of publication in another place. In that report the data will be presented in detail, with probable errors, etc.

[2] Cf. for summary and bibliography of earlier papers Stockard, C. R., and Papanicolaou, G., "A Further Analysis of the Hereditary Transmission of Degeneracy and Deformities by the Descendants of Alcoholized Mammals," *Amer. Nat.*, Vol. L., pp. 65–88 and 144–177, 1916.

[3] Cf. Cole, L. J., and Bachhuber, L. J., "The Effect of Lead on the Germ Cells of the Male Rabbit and Fowl as Indicated by their Progeny," *Proc. Soc. Exper. Biol. Med.*, Vol. XII., pp. 24–29, 1914.

II. Material and Methods.

General Plan.

The general plan of this investigation involves some features which have not been incorporated in earlier researches in this general field. In the first place, it was thought desirable to use *two* pure breeds of poultry for the foundation stock in the experiments rather than one, and in consequence of this make the offspring of the treated animals F_1 crossbreds rather than pure-bred birds. The primary consideration in favor of this plan was that, by its adoption, a much more manifold opportunity seemed likely to be given to test any putative influence of the poisons on the germ plasm. It should be possible in an experiment of this sort to see whether in F_1 the usual conditions as to Mendelian dominance are in any manner or degree disturbed by the administration of the poisons to the parents. Further, when the F_1 individuals from treated parents are themselves bred there will be an opportunity to apply the most delicate of all genetic tests for the composition of the germ plasm, namely the test of segregation in F_2 and succeeding generations.

In the investigation here reported the foundation stock used came from pedigreed strains of two breeds, Black Hamburgs and Barred Plymouth Rocks. Both of the strains used have been so long pedigree bred by the writer, and used in such a variety of Mendelian experiments, that they may be regarded as "reagent strains," whose genetic behavior under ordinary circumstances may be predicted with a degree of probability amounting practically to complete certainty. Furthermore the results of crossing these two breeds reciprocally have been thoroughly studied by the writer.

Substances Used and Mode of Administration.

In the present investigation three different series of birds were started. To the birds in one series was administered 95 per cent. ethyl alcohol. To those in the second series was administered methyl alcohol, and to those in the third series, ether.

The method followed in these experiments for the administration of the poisons was essentially that which has been used by Stockard, namely the method of inhalation.

In the present experiments inhalation tanks of two different sizes have been used. They are essentially square boxes of galvanized iron, having at the top a round opening which serves as a means of entrance and exit for the bird. This opening is tightly closed by a cover during an experimental treatment. Below the bottom of the tank is a cylindrical reagent chamber closed by a tight fitting cover from below. In this projection below the floor of the tank proper is placed absorbent cotton saturated with the particular reagent used. Over the top of the reagent chamber is placed a piece of heavy galvanized wire gauze of about half-inch mesh which serves to complete the floor of the inhalation compartment proper, without obstructing the diffusion of the fumes from the reagent chamber.

Regarding the mode of administration of the poisons used it was found early in the work to be undesirable to depend entirely upon the evaporation of the reagent from cotton in the chamber at the bottom of the tank. This process took altogether too long a time to saturate the air of the tank with the vapor. Practically from the beginning we have used a combination of this method plus a preliminary saturating of the air with the vapor of the substance used by means of an atomizer. The routine procedure is this: there is placed in the reagent chamber at the bottom of the tank a piece of absorbent cotton soaked with the reagent to be used, ethyl or methyl alcohol or ether, as the case may be. Then the operator quickly but thoroughly fills the whole of the tank proper by means of an atomizer with a saturated vapor of the same substance. The birds to be treated are then introduced quickly, allowing as little as possible of the vapor to escape in the process. When the birds have been introduced the cover of the tank is tightly closed and left in that condition for one hour. It is to be understood throughout this paper that every bird designated as a "treated bird" has spent one hour every day in one of these tanks subjected to the fumes of the reagent specified in the particular case.

The number of treated birds used in the experiments to the date covered in this report is 19. The number of untreated control brothers and sisters is 58.

III. Results.

A. In the Treated Individuals.

Before entering upon any discussion of the effect of the alcohol treatment on the progeny it seems desirable to examine with some care into the effects, both structural and physiological, upon the treated individuals themselves. In this examination attention will be confined to characters which are capable of quantitative definition and measurement. The main results are summarized in Table I.

TABLE I.

Showing in Summary Form the Effect of Continued Administration of Alcohol (Ethyl and Methyl) and Ether, by the Inhalation Method, upon the Treated Individuals Themselves.

Character or Quality Studied.	Treated Individuals.	Untreated Controls.	Net Result on Alcoholists.
1. Mean number per bird of consecutive days of treatment	344.2	0	
2. Net percentage mortality (to Feb. 1, 1916) exclusive of birds accidentally killed	0	41.0	+
3. Mean body weight of females (in gms.)	3266	**2953**	—
4. Mean egg production per bird, 14 months	183.97	180.80	0
5. General activity	Reduced	*Normal*	—
6. Sexual activity	Reduced	*Normal*	—

The plan of this table is as follows: In the last column of the table a plus sign denotes that, with reference to the particular character discussed, the alcoholists have been favorably affected; a minus sign that they have been unfavorably affected as compared with untreated controls. A zero indicates that no effect of the treatment, one way or the other, has been detected.

From these summarized data it is possible to gain a tolerably clear comprehension of the objective happenings in these experiments so far. The treated animals themselves are not *conspicuously* worse or better than their untreated control sisters or brothers. The survivors, *i. e.*, those not killed by accident, are after roughly a year and a half of daily treatment, becoming a bit too fat for their best physiological economy, but except for that point, and the reduced activity which goes with it, they are very much like normal fowls.

Their apparently much better mortality record is indeed conspicuous, but in view of the small numbers involved, no great significance can be attached to it. It is probable that with larger numbers of birds as the experiments proceed this apparent superiority in relative mortality will disappear or be much reduced.

Regarding egg production the following details are of interest:

The egg production of the treated birds and the untreated controls was entirely normal in respect of its seasonal distribution, as well as in regard to its amount.

There has been no significant difference in the egg production of the treated birds and their untreated control sisters, either in the total average number of eggs produced per bird, or in the seasonal distribution of this production. Taking the whole untreated flock, the mean production per bird in the 15 months was 184.74 eggs, while the mean production for the treated birds was 183.97, making a difference of 0.77 egg in favor of the untreated. Taking the "special control" mean of 180.80 eggs there is a difference between this and the treated of 3.17 eggs in favor of the treated. Obviously the only conclusion which can be drawn from these insignificant differences is that the inhalation treatment has not affected the egg production of the birds, either favorably or adversely.

During the months of July, 1915, to October, 1915, inclusive the mean production of the treated birds fell below that of the control sisters. The difference between the two curves in this region, however, is no greater than may at any time occur between two similarly managed groups of sisters, according to the writer's experience with egg records. There appears to be no reason to attach any significance to this dip of the treated below the control curve. Taking the whole period covered by the report it is clear that the two curves wind about one another, now one, now the other being uppermost, just as curves for two random samples of the same material would be expected to do.

B. *In the F_1 Progeny of Treated Individuals.*

In this section of the paper it is proposed to discuss the effects, so far as any are observable, of the alcoholization of one or both of the parents upon the progeny in the first generation. Different characters of the progeny will be considered, and as before primary attention will be given to such characters as admit of quantitative expression.

1. *Plan of Matings in 1915.*—The alcoholized birds and the untreated controls were mated early in February, 1915. Eggs were saved for incubation from these matings from about February 15.

The general plan of the matings in 1915 was to breed a treated male of each of the three classes, ethyl, methyl and ether, with (*a*) untreated control females, and (*b*) with treated females of his own class (*i. e.*, ethyl ♂ × ethyl ♀, methyl ♂ × methyl ♀, ether ♂ × ether ♀). In addition to these matings an untreated control male was mated with (*a*) untreated control females, (*b*) ethyl females, (*c*) methyl females, and (*d*) ether females.

All of the matings were of the type Black Hamburg ♂ × Barred Plymouth Rock ♀. There were produced 234 chicks from matings wherein one or both parents were treated.

2. *Germinal Dosage Index.*—In the present investigation the following reasoning has been used in devising a numerical expression of the dosage, so far as concerns the progeny. Two germ cells, a sperm and an ovum, unite to form the zygote of each progeny individual. It is proposed to designate as the "total germ dosage index" the total number of days during which the two gametes making the offspring zygote have been exposed to alcoholic influence while sojourning in the body of the treated individuals. Such a germ dosage index could, of course, be calculated for each individual progeny chick born. It seems, however, more desirable for present purposes to combine the figures for each mating, and take the sum of the number of days from the beginning of treatment of the male parent to the *average* date of hatching of the progeny, plus the number of days from the beginning of treatment of the female parent to the *average* date of hatching of the progeny as the germ dosage index for that mating. This can be expressed in a formula as follows:

$$\textit{Total germ dosage index in days} = (M_h - A♂) + (M_h - A♀)$$

where

M_h = Mean date of hatching of progeny.

$A♂$ = Date when treatment of ♂ parent began.

$A♀$ = Date when treatment of ♀ parent began.

The total germ dosage index for the F_1 progeny in these experiments ranges from 130 days to 354 days with the matings for the different substances used well scattered over the range.

3. *The Fertility and Hatching Quality of the Eggs from Alcoholized Parents.*—One of the surest and most delicate indicators of constitutional vigor and vitality in poultry which has yet been discovered is the hatching quality of the eggs. Anything which upsets the general metabolic balance or impairs the vitality of either partner in a mating will show its effect in a diminished hatching power of the eggs from that mating. In view of these facts an examination of the data relative to this character in these alcoholic matings becomes of especial interest. A summarized statement of the effects on the progeny is given in Table II.

TABLE II.

Showing in Summary Form the Effect of Continued Administration of Alcohol (Ethyl and Methyl) and Ether, by the Inhalation Method, upon the Progeny.

Character Studied.	Offspring of				Net Result on Alcohol Offspring.
	Treated ♂♂ × Untreated ♀♀.	Treated ♂♂ × Treated ♀♀.	All Treated Parents.	Untreated Controls	
1. Mean germ dosage index..	137.8	299.0	210.35	0	
2. Percentage of infertile eggs (*i. e.*, eggs in which no zygote was formed).....	25.2	59.2	41.7	**25.3**	—
3*a*. Percentage of embryos dying in shell............	36.6	**26.9**	33.3	42.2	+
3*b*. Percentage of fertile eggs (*i. e.*, zygotes) which hatched...............	63.0	**72.3**	66.7	57.8	+
4. Percentage of all eggs which hatched...............	47.1	29.4	38.6	**44.4**	—
5. Percentage mortality under 180 days of age........	21.1	**10.6**	17.6	36.9	+
6. Percentage mortality over 180 days of age........	**5.9**	13.6	10.3	15.3	+
7. Sex ratio: per cent. ♂♂..	48.9	45.5	47.7	50.0	0
8. Mean hatching weight per bird, males............	34.91	**36.97**	—	34.24	+
9. Mean hatching weight per bird, females...........	35.04	**37.17**	—	34.73	+
10. Mean adult weight per bird, males.................	2,669	**2,815**	—	2,392	+
11. Mean adult weight per bird, females...............	2,020	**2,063**	—	1,928	+
12. Percentage of weak or deformed chicks..........	0.7	**0**	0.4	1.0	+
13. Abnormalities of Mendelian inheritance............	0	0	0	0	0

Summarizing the general features of the above results regarding production of offspring by alcoholized parents it may be said that the average percentage fertility of eggs is diminished and the average hatching power of the fertile eggs is increased after alcoholization of the parents. The reduction in average fertility of the eggs is due chiefly to the effect on the germ cells of the males and females, whose sexual activity is in general somewhat diminished by the treatment. Also alcoholized females are not as attractive to the males as untreated and hence are discriminated against in the matings, and furthermore probably the oviduct of the treated female does not furnish quite so favorable an environment for sperm as the oviduct of untreated females. The net result is that alcoholized parents produce on the average fewer offspring per mating unit than do normal, untreated parents under conditions otherwise similar.

4. *Mortality of F_1 Chicks.*—According to the results of earlier work in this general field it would be expected that there would be a decidedly higher rate of mortality among the offspring of the alcoholized parents than the normal.

Taking all the evidence of the present experiments into account, it admits of no doubt that the probability that a chick on the Maine Station's poultry range in 1915 would survive to maturity was not diminished, but, on the contrary, was in general substantially *increased,* if that chick's parents had both been subjected to a daily dosage of alcohol for from four to seven months before it was hatched. Since the chicks from treated parents were indiscriminately mixed with those from normal parents in housing, yarding, feeding, watering, etc., the fact that the former sort of chicks showed a lower mortality than the latter sort cannot be attributed to differential treatment after hatching.

5. *The Sex Ratio in the F_1 Progeny of Alcoholized Parents and Normal Parents of the Same Breeds.*—It has been claimed at various times and by various persons that the general metabolic condition of the parents at the time of conception is a factor in sex determination, or at least has an influence on the sex ratio.

The figures give no ground for asserting that the relative proportions of the sexes produced are significantly different in the alcoholic and normal control series. If the treatment has had an influence on this character it has been so slight as not to be statistically discernible in samples of the size here dealt with.

6. *Hatching Weight of F_1 Progeny.*—In the present series of experiments there is no significant difference in mean hatching weight between the offspring of treated males and the offspring of normal untreated control males when both are mated to normal untreated females. The slight differences which do appear are of the same order of magnitude as their probable errors.

Both the male and the female offspring of matings in which both parents were treated have a larger mean hatching weight (*i. e.*, are heavier when hatched) than the offspring of either completely normal control matings, or of matings in which the father only is treated. The differences here are relatively large and are statistically significant in comparison with their probable errors.

7. *Growth of the F_1 Progeny.*—Growth, as measured by increase in body weight, is universally recognized by physiologists and by practical animal husbandmen as one of the most valuable indices of innate constitutional vigor and vitality which it is possible to obtain. On this account it was thought to be of first-class importance to study the growth of the offspring from alcoholized as compared with untreated parents.

The offspring of alcoholized parents, whatever the nature of the mating, showed a higher mean adult body weight than offspring of untreated parents of the same breeds mated in the same way. This is true of both sexes.

In the case of the male chickens there was no substantial difference in the rate of growth in the three lots until after an age of about 100 days was passed. From that point on the male offspring of treated ♂♂ × untreated and treated ♀♀ grew at a more rapid rate than the controls. The differences in mean body weight for a given age became increasingly large as the age advanced. At 200 days of age we have by interpolation on the curves the following set of comparative mean body weights.

Comparative Mean Body Weights at 200 Days of Age.

	Absolute Weight.	Relative Weight.
Males *ex* untreated ♂♂ × untreated ♀♀	2,392.32 gm.	100
Males *ex* treated ♂♂ × untreated ♀♀	2,668.97 gm.	112
Males *ex* treated ♂♂ × treated ♀♀	2,815.25 gm.	118

In the case of the female chickens there was no substantial difference in the rate of growth in the three lots until after an age of about 150 days was passed. During the next 25 days the controls grew faster than the chicks from treated parents. At and after 200 days of age, however, the offspring of treated parents (one and both) showed a higher mean body weight than the controls. We have the following set of comparative mean body weights at 250 days of age, obtained by interpolation on the curves.

Comparative Mean Body Weights at 250 Days of Age.

	Absolute Weight.	Relative Weight.
Females *ex* untreated ♂♂ × untreated ♀♀	1,927.72 gm.	100
Females *ex* treated ♂♂ × untreated ♀♀	2,020.38 gm.	105
Females *ex* treated ♂♂ × treated ♀♀	2,062.98 gm.	107

At all ages in the case of the male chicks, and in all ages but two (12.5 and 19.5 days) in the case of the female chicks, the mean body weight of the offspring having both parents alcoholic was higher than that of the offspring having one parent only, the father, alcoholic. The differences are, for the most part, insignificant in comparison with their probable errors, but the uniformity with which the "both parents treated" curves maintain their superiority over the "father only treated" curves is noteworthy, and significant.

There are no distinctive differences in relative variability between the three different lots of chicks. In general the relative variability tends to diminish after an age of about 30 days is past.

The evidence derived from a study of the growth of the chickens in this experiment lends no support to the view that parental alcoholism necessarily reduces the vitality of the offspring or induces degeneracy. On the contrary the data plainly indicate that the offspring of alcoholized parents are in some degree superior in vigor and vitality to those from untreated parents.

8. *Deformities in the F_1 Progeny.*—One of the most striking features of Stockard's results on the alcoholization of guinea pigs is that a considerable percentage of the progeny of treated parents exhibit gross malformations of various organs, particularly the eyes. In the present experiments with poultry, nothing of this sort has made its appearance. The proportion of such abnormal chicks

produced in the breeding season of 1915 from alcoholized parents was no greater than the number produced from untreated parents. In actual fact there was exactly *one* chicken out of 234 hatched from alcoholized parents in 1915 that was too weak to band, and was in consequence killed at the time of hatching. None was deformed. Out of 1,527 chicks from untreated parents, 16, or 1.0 per cent., were weak or deformed or both.

Discussion of Results.

We have seen that *out of 12 different characters for which we have exact quantitative data, the offspring of treated parents taken as a group are superior to the offspring of untreated parents in 8 characters.* The offspring of untreated parents are superior to those of the alcoholists in respect of but two characters, and these are characters which are quite highly correlated with each other and really should be counted as but a single character. Finally with respect to two character groups there is no difference between the alcoholists and the non-alcoholists. The character groups which have been dealt with in this study, and for which definite *quantitative* data are herein presented, seem to cover a much wider range of physiological and genetic factors and phenomena than has ever been included or even approached in any previous study regarding the effects of parental alcoholism upon the progeny. They have the further advantage of being characters which are measurable (either statistically or otherwise) and on that account greatly reduce, if they do not entirely eliminate, the possibility of personal bias or prejudice influencing the results.

The mutual accordance of the results from characters involving such a manifold range of physiological factors is striking. This fact in considerable degree offsets the fact that as yet our series of experimental animals is statistically small, leading to such large probable errors that the individual differences are not in every case significant in comparison with their probable errors. The experiments are of course being continued and expanded, and concurrently the probable errors of differences are being reduced. If results in the same sense as the present ones continue to appear (as seems to be the case) they are bound presently to become very convincing to such persons as are not prevented by prejudice from accepting or appreciating scientific evidence on the problem of the effect of parental alcoholism upon the progeny.

We may evaluate our results in general terms as follows:

1. There is no evidence that *specific* germinal changes have been induced by the alcoholic treatment, at least in those germ cells which produced zygotes.

2. There is no evidence that the germ cells *which produced zyygotes* have in any respect been injured or deleteriously affected.

3. The results with poultry are in *apparent* contradiction to the results of Stockard, Cole and others with mammals. I believe, for reasons which will presently appear, that this contradiction is only apparent and not real, paradoxical as such a statement may appear.

4. The results with poultry are in a number of important respects in essentially complete agreement with those of Elderton and Pearson[4] on parental alcoholism in man, and of Nice[5] in mice.

The interpretation of these results which seems to account best for all the facts is that the apparent discrepancy between the avian and mammalian results is fundamentally due to a difference in degree of resistance of the germ cells to alcohol. On this basis it is possible, I believe, to frame an hypothesis which will bring together in a satisfactory manner under one point of view the apparently discrepant results of Stockard, Pearson, Nice and the writer.

At the outstart let us remind ourselves of a point which one is apt to overlook in considering results of this sort, namely that the germ cells which produce the zygotes, which are the progeny of our experiments, are only a very minute fraction of all the germ cells which the parents produce. Let X be the total number of germ cells (ova or spermatozoa) which the individual produces, and let a be the number which succeed in taking part in the formation of

[4] Elderton, E. M., and Pearson, K., "A First Study of the Influence of Parental Alcoholism on the Physique and Ability of the Offspring," Eugenics Lab. Mem., X., pp. 1–46, 1910. (Second edition.)

[5] Nice, L. B., "Comparative Studies on the Effects of Alcohol, Nicotine, Tobacco Smoke, and Caffeine on White Mice. I. Effects on Reproduction and Growth," *Jour. Exper. Zool.*, Vol. 12, pp. 133–152, 1912.

a zygote, and let A be the number which do not so succeed. Then, of course, $A = X - a$, or put the other way about,

$$X = A + a.$$

This is the fundamental gametic equation. We know that A is enormously greater than a. There is furthermore a great deal of evidence that a is not a random sample of X, but on the contrary is a highly selected sample. To Roux in his "Kampf der Theile" is to be given the credit for first pointing out what now seems axiomatic, that there is constantly going on a struggle for survival among the cells of the organism, the physiologically "best" being the survivors. To the philosophical breeder of animals nothing seems more certainly established than that this process of selection is constantly going on and is of very special importance among the germ cells. Direct and convincing observational and experimental proof of it has been given by the double mating experiments which Cole and Davis and Cole and Bachhuber have carried out.

Granting the existence of variation in the vigor or resisting power of germ cells we have the necessary basis for the action of a selective agent. The hypothesis which we wish to suggest is that alcohol acts as such a selective agent upon the germ cells of alcoholized animals. The essential points in such an hypothesis may be put in the following way.

1. Assume the *relative* vigor, or resisting power of germ cells varies or grades continuously from a low degree, say 1, to a high degree, say 10, and further assume that the *absolute* vigor of the whole population of germ cells, measured by the mean let us say, is different for different species.

2. In the intensity of dosage employed in inhalation experiments alcohol does not destroy or functionally inactivate *all* germ cells. The proportionate number of the whole population of germ cells which will be inactivated by such dosage may fairly be supposed to depend upon the mean *absolute* vigor or resisting power characteristic of the particular species or strain used. In a species with germ cells of absolutely low mean vigor proportionately more will be functionally inactivated than in a species of high absolute mean vigor of germ cells.

3. Besides the germ cells which are wholly inactivated by the

deleterious agent, and which we may designate as class (*a*), we may fairly assume that there is a possibility of two other classes existing, viz., (*b*) germ cells which, while not completely inactivated, are so injured by the agent as to produce zygotes which are measurably defective in some degree, and (*c*) germ cells which are not measurably affected by the agent at all in the dosage employed, and produce zygotes which are not discernibly otherwise than perfectly normal.

4. It appears entirely fair to assume that germ cells of the (*a*) class are of relatively the lowest mean vigor or resisting power, class (*b*) next, and class (*c*) the highest. The proportionate number of the two sorts of zygotes corresponding to classes (*b*) and (*c*) of germ cells which would be expected to appear in any experiments made to test the point would clearly be a function of the mutual relationship or proportionality between two variables, the dosage of the deleterious agent on the one hand, and the mean absolute resisting power of the germ cells characteristic of the strain or species of animal used in the experiments on the other hand.

5. If the dosage of the agent be relatively *high* in proportion to the mean absolute resisting power it would be expected that all the germ cells would fall into classes (*a*) and (*b*), producing no zygotes at all or zygotes in *some degree* defective. This about represents the condition, so far as can be judged from the data given, with Stockard's alcoholized guinea pigs and Weller's[6] lead-poisoned guinea pigs. The dosage is sufficiently high in proportion to the absolute germinal resisting power that all or practically all of the offspring are defective in greater or less degree and in reference to some one or more characters. Stockard's F_2 and F_3 results indicate that though the untreatd F_1 animals from alcoholists may appear normal, they really are somewhat defective.

6. If, on the other hand, the dosage, though *absolutely* the same, be relatively *lower* in proportion to the mean absolute resisting power of the germ cells it would be expected that all three germ cell classes (*a*), (*b*) and (*c*) would be represented. The zygotes actually formed would be chiefly produced by (*c*) germ cells, and to a much smaller extent by (*b*) cells. Under these circumstances it would necessarily follow that a random sample of the zygotes

[6] Weller, C. V., "The Blastophthoric Effect of Chronic Lead Poisoning," *Jour. Med. Research*, N. S., Vol. XXVIII., pp. 271–293, 1915.

produced *after* the action of the deleterious agent would, on the average, be superior in respect to such qualities as growth, etc., which may be supposed to depend in part at least upon germinal vigor, to a random sample of zygotes formed *before* the action of the agent, because the germ cells of class (*c*) are a selected superior portion of the total gametic population.

7. Essentially that proportionality between effective dosage of the deleterious agent and absolute resisting power of the germ cells outlined in the preceding paragraph (6) is believed to have obtained in the present experiments with fowls, Nice's experiments with mice, and nature's experiments with the workingmen's populations studied statistically by Elderton and Pearson.

There is much detailed evidence which can be adduced from my own experiments and from the literature in support of the above hypothesis. This evidence will be discussed in the complete paper.

Finally, I wish again to emphasize that, in my opinion, the results here set forth are not contradictory to those of Stockard. Anyone who bases a criticism of his results on the present experiments will go beyond the facts. Our results seem to me to be supplementary to those of Stockard, and to throw an interesting light on the need for caution in reaching a correct interpretation of all experiments in which a mildly deleterious agent acts upon the organism. It would seem clear that there is need for caution in this difficult field. If the conclusions as to the utterly dreadful and relentlessly certain effects of parental alcoholism on the progeny which have been transported, as it seems to me somewhat recklessly, from Stockard's guinea pigs to human beings, were really true for the latter, then I can see no escape from the further conclusion that a great majority of the individuals belonging to the higher intellectual and social classes in the countries of Western Europe today ought to be blind, dwarfed, and degenerate wretches, because social history gives definite and uncontrovertible evidence that their parents and their grandparents on the average consumed proportionately as much and probably more alcohol than the corresponding generations of Stockard's guinea pigs. The absence of general degeneracy in these social classes could not be more completely and scientifically demonstrated than it has been by the events of the past two years.

The experiments here reported are being continued.