exactly duplicates in all essential features the urinary findings in the later stages of severe types of diabetes mellitus. The dextrose to nitrogen ratio is approximately 3.6 upon a carbohydrate free diet. Glucose given at this time was quantitatively recovered. In spite of doses of sodium bicarbonate ranging from 20 to 30 grams per day the ammonia output rose to over four grams per day, representing 27 per cent. of the total nitrogen at its highest level. Oxy-butyric acid, diacetic acid, and acetone were eliminated in large amounts. When large quantities of glucose were given the urine picture returned to normal almost at once, and the diabetes completely ceased when phlorhizin administration was stopped, the patient rapidly returning to normal condition. Considering the severity of the treatment the patients stand it surprisingly well. They lose weight, but the general condition does not at all duplicate the later stages of diabetes mellitus.

The findings in this case will be reported in detail elsewhere.

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A study of further generations of mammals from ancestors treated with alcohol.

By CHARLES R. STOCKARD.

[*From the Department of Anatomy, Cornell Medical School, New York City.*]

Experiments now in progress for almost four years have demonstrated the fact that the germ cells of male guinea-pigs can be so injured by allowing the animals to inhale the fumes of alcohol that they give rise to defective offspring although mated with vigorous untreated females.[1]

In the present communication I wish to emphasize the fact that the effect of this injury of the germ cells is not only shown by the immediate offspring of alcoholized animals but is conveyed through their descendants for at least three generations.

The offspring from the treated guinea-pigs which reach ma-

[1] *Archiv f. Entw.-Mech.*, XXXV, 1912; *Archives of Int. Med.*, X, 1912; *American Nat.*, XLVII, 1913.

turity are usually nervous and slightly under sized. These animals F_1, or the second generation, are never themselves subjected to the fume treatment. Mated even with normal animals the results are poor when compared with the outcome of normal control matings. Twenty-six matings of second generation with normal animals gave in 4 cases negative results or early abortions, 2 stillborn litters of 4 individuals and 20 living litters containing 31 young, 19 of which died and only 12 survived. Twenty-two matings of second generation by alcoholized animals gave 5 negative results or early abortions, 3 stillborn litters of 7 young and only 14 living litters consisting of 25 young, 11 of which died and 14 survived.

If second generation animals, non-relatives in most cases, are mated with one another the sum total of the result is worse than when they are mated in either of the above combinations. Forty-seven such matings gave in 14 cases negative results or early abortions, 3 stillborn litters containing 8 young, and only 30, less than 64 per cent., living litters consisting of 46 young; 14, or about 33 per cent., died soon after birth and 32 survived.

A point of interest is that several of these offspring, F_2, or third generation, show gross defects or deformities. Only two of the immediate offspring from alcoholized animals have shown a clouded condition of the cornea of one eye, and no defect or deformity of any nature has been observed in 89 control young. However, among the 54 F_2, or third generation, young that have reached term 9 or about 17 per cent. show gross eye defects. Two had opaque corneas, 3 complete cataracts in both eyes, the lens being milk white, 2 had one normal eye while the other was about half size and blind, one has only one eye, that of the opposite side being completely absent, and finally one animal was entirely eyeless, having no indication of eyeballs, optic nerves or chiasma.

These abnormal animals arose from parents that had not been subjected to the alcohol treatment, although in all cases two or more of their grandparents, and usually only the paternal ones had been treated for various lengths of time with the fumes of alcohol.

Only a few matings of the third generation, F_2, animals have been made, yet if conclusions may be based upon these small

numbers the outcome is more unfavorable than from second generation matings. Six such matings gave in 2 cases negative results or early abortions, 1 litter of 2 stillborn young and 3 living litters containing 5 animals, only 1 of which survived, 4 dying soon after birth.

Two of the four were completely eyeless, the eyeballs, optic nerves, and chiasma being absent. There was an abortive attempt at eyelid formation, a well-formed lachrymal gland and the extrinsic eye muscles were present. These defects no doubt result from injury inflicted upon the germ cells by the experimental treatment. The parents of the anophthalmic guinea-pigs just mentioned were untreated, the four grandparents were also untreated but their great-grandfathers were all alcoholized and their great-grandmothers were all normal animals. It thus appears that the injury received by the germ cells of the great-grandfathers was responsible for the defective condition of their descendants. Many of the defective young have normal maternal ancestry and alcoholized paternal ancestors, the reverse being also true.

Although the descendants of alcoholized males seem to transmit the defects through subsequent generations even more decidedly than the offspring of treated females, yet it is peculiar to find that in pairing F_1, second generation, animals with normal mates if the male of the pair be F_1 the resulting offspring are better and more vigorous than when an F_1 female is mated with a normal male. Eleven matings of F_1 males with normal females gave 1 negative result, 1 stillborn litter of 2 young and 9 living litters of 11 young, 9 of which survived but later gave rise to defective descendants. Fifteen matings of F_1 females with normal males gave 3 negative results, 1 stillborn litter of 2 young and 11 living litters containing 20 young, only 3 of which survived; a result many times more disastrous than that derived from the previous combination.

Since the direct action of the alcohol fumes on the cornea of the eye finally renders many of the treated animals blind one might imagine some connection between this and the defective eye condition of the offspring and their descendants, yet such is certainly not the case. The defective eyes of the descendants

of treated animals are due to a generally weakened or impaired development. The male germ cells are weakened or injured by the alcohol treatment and all individuals arising from combinations involving such a germ cell are below normal. In this connection Cole and Davis[2] have recently recorded an interesting experiment with rabbits. They sought to control the experiments on the effects of alcoholic inhalations in a very ingenious way. "By breeding a male homozygous for color and an albino male both to an albino female it is possible to assign the young to their respective fathers, since the offspring of the colored male will be colored and those of the albino male will be albinos. If one of the males now be alcoholized while the other is normal, and offspring from both result, any differences, such as defects in the offspring, may safely be attributed to the effects of the alcoholizing of the male, since both sets of fetuses have developed in the same uterus at the same time, and consequently there can be no question of different environmental influences."

A preliminary test of 36 double matings was made in which both males were normal. One pigmented male was used in 23 of these matings, an albino male also being used in each case—190 offspring were produced and the albino male sired only 24 of them, 166 coming from the pigmented sire. This showed a strong individual potency for the colored male. Yet after he had been alcoholized, by the inhalation method, *he failed to sire any offspring at all* when used in conjunction with an albino male, although he was bred to the female first in at least 5 of the 7 matings made. When bred alone to normal females he sired several litters of young which later showed certain indications of defects. These experiments demonstrate conclusively that the spermatozoön is actually weakened or disabled by the alcohol treatment, as I had formerly concluded in explaining the defective offspring from alcoholized male guinea-pigs.

[2] *Science*, N. S., XXXIX, 1914.