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THE RELATION OF VITAMIN A TO ANOPHTHALMOS IN PIGS

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Forty-two pigs (four litters) were born blind at the Texas Agricultural Experiment Station in the course of experiments relating to maternal vitamin-A deficiency. Other defects noted were cleft palate, cleft lip, accessory ears, and arrested ascension of the kidneys. Definite and complete genetic tests were made to determine whether or not an hereditary factor was responsible for the eye anomaly and close matings such as blind brother x blind sister, and normal mother x blind son, produced only normal pigs. These studies leave no reasonable doubt that maternal deficiency of vitamin A will result in a variety of defects in the offspring, including blindness and even a failure of complete development of eye tissue, together with those above-mentioned.

The normal mothers of these blind pigs were depleted to a very low state of vitamin A before breeding and were continued on the vitamin-A-free ration for the first 30 days of the gestation period (the time during which the eye develops in the pig embryo).

Vitamin-A deficiency is by no means uncommon in human diet and it may easily be that many of the eye weaknesses which we suffer today are due to maternal vitamin-A deficiency, just as Dr. H. M. Taylor has recently discovered that some of the deafness among Southern children is due to quinine taken by the mother during pregnancy. In any case, it is obvious that until we have evidence to the contrary, we should insist on an abundance of vitamin A in the diet of the expectant mother in the early stages of pregnancy when so many of the vital organs of the embryo are being formed. From the Division of Swine Husbandry, Texas Agricultural Experiment Station. Read before the Association for Research in Ophthalmology, Atlantic City, June 11, 1935.

Numerous publications have appeared relative to the effect of vitamin A on the health of the individual from birth to maturity, and also relative to the health of mature animals and human beings. Osborne and Mendel showed as early as 1913 that if vitamin A is withheld from the ration or diet, the subject will eventually contract a disease of the eye, variously known as ophthalmia, xerophthalmia, keratomalacia, conjunctivitis, or keratoconjunctivitis. It has been shown also that the nerves of animals degenerate when the ration is without vitamin A, but the literature is lacking concerning the relation of maternal vitamin-A deficiency to embryonic development.

In connection with an investigation on the effects of vitamin A on swine, at the Texas Agricultural Experiment Station, a gilt of the Duroc breed that had been fed a vitamin-A-free ration for a period of 160 days before breeding, and for the first 30 days after breeding, farrowed in 1932, a litter of eleven pigs, all of which were born without eyeballs, so far as could be determined by macroscopic examination.

Since anomalies of this nature had not previously been observed in this particular herd in the many years that it has been under observation, and since the ration fed to this gilt was deficient in vitamin A, the natural inference must be that the eye anomaly of the young pigs was in some way associated with maternal vitamin-A deficiency. Further experiments were immediately initiated to determine the relation between vitamin A and embryonic eye development.

Two gilts were placed on a vitamin-A-free ration in an attempt to duplicate this anomaly. At the same time, two other gilts were fed the vitamin-A-free ration, plus one percent of cod-liver oil. These two latter gilts were bred 154 days after they were started on test, and farrowed normal litters in March, 1933. One of the gilts fed on the vitamin-A-free ration failed to show the symptoms of estrus, while the other one was bred 160 days after she was

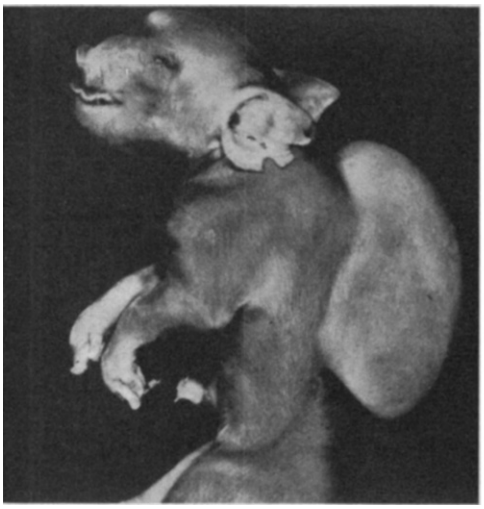

Fig. 1 (Hale). Showing pig without eyeballs, farrowed June 8, 1934, out of Dam No. 336. Note subcutaneous cysts on head and back.

Fig. 2 (Hale). Showing pig with double cleft lip, farrowed June 8, 1934, out of Dam No. 336. This pig was also born without eyeballs.

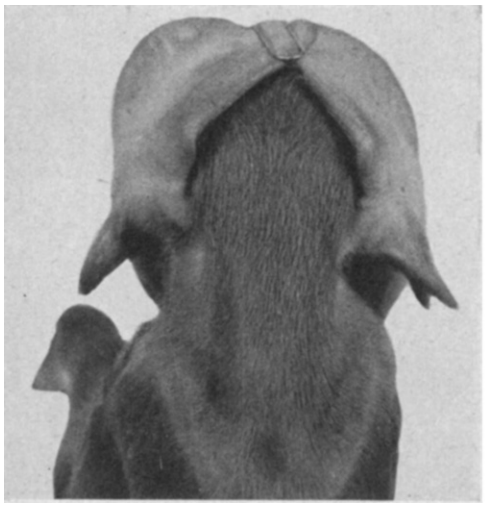

Fig. 3 (Hale). Showing pig with extra earlike growths, farrowed May 11, 1935, out of Dam No. 49. This pig was also born without eyeballs.

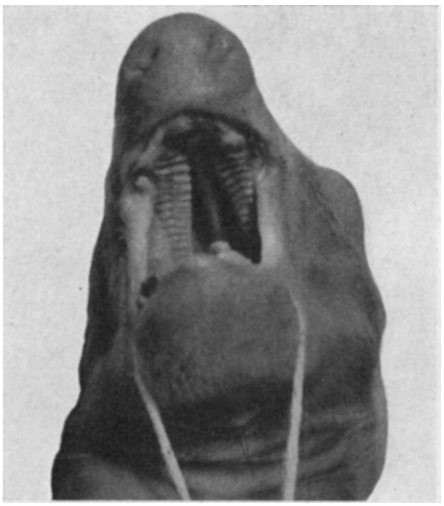

Fig. 4 (Hale). Showing pig born with cleft palate, farrowed May 11, 1935, out of Dam No. 49. This pig was also born without eyeballs.

started on the vitamin-A-free ration, but failed to farrow at the end of the normal gestation period. A post-mortem examination by Schmidt indicated the litter had probably perished at an early stage, followed by complete resorption of the fetuses.

In 1933, two additional five-months-old gilts, weighing 102 and 116 pounds respectively, were placed on the vitamin-A-free ration. The gilts were self-fed in a dry lot, and had access to sunshine. On the 176th day after starting on feed, one of the gilts was so completely affected by the depletion of vitamin A that she was unable to get up. A two-ounce dose of cod-liver oil was administered, and she regained her strength so rapidly that she was able to walk within eight hours following the cod-liver-oil treatment. Both gilts were bred to a sire of the Duroc breed on the 190th day after starting on feed. It will be recalled that the litter with the eye defects farrowed in 1932 was sired by an Essex male, which is an altogether different breed. Symptoms of vitamin-A deficiency in the gilts at the time of breeding were evidenced by their wobbly gait, weaving, and crossing of the hind legs at the walk, drooping of the ears, and loss of weight. After the gilts were bred, they remained on the vitamin-A-free ration for the first 30 days of the gestation period, the time during which it is known that the eye develops in the pig embryo. After the first 30 days of the gestation period had passed, the gilts were given an abundance of vitamin A in the form of cod-liver oil, so as to furnish them every opportunity to complete a full gestation period.

On June 8, 1934, both gilts farrowed. The gilt that had gone through the entire 190 day period without vitamin A farrowed a litter of ten pigs. A macroscopic examination showed that all these pigs were born without eyeballs, an exact duplicate of the litter produced under similar conditions in 1932. The gilt that had received a single dose of cod-liver oil two weeks before conception, farrowed fourteen pigs. In this litter, macroscopic examination showed various combinations of eye defects; some with no eyes; some with one eye; some with one large and one small eye; but all were blind. Three pigs of this litter, all blind, were raised to maturity on a normal ration. In both litters, various other defects were also observed, such as accessory ears, subcutaneous cysts, hare lip, and misplaced kidneys.

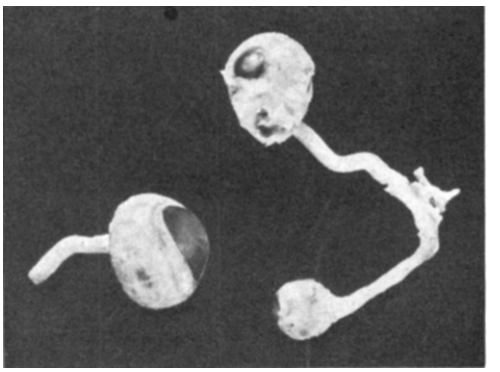

Fig. 5 (Hale). Showing normal eye of pig (A), and a pair of defective eyes (B). The anomaly was from a pig farrowed June 8, 1934, out of Dam No. 187. Both the normal eye and the pair of blind eyes were removed from ten-months-old pigs.

Finally, on July 6, 1934, another five-months-old gilt weighing 106 pounds was placed on the vitamin-A-free ration, and fed under the same conditions as those previously described. She was bred 192 days after starting on test, to a Duroc male unrelated to any other sire used in these tests, and on May 11, 1935, she farrowed seven pigs, all without eyeballs, as determined macroscopically. Other defects observed in the pigs were: hare lip, cleft palate, accessory earlike growths at the base of the ear, malformed hind legs, and a failure of the kidneys to ascend from their embryonic position.

It might be assumed that the eye anomalies here described are due to heredity; that the genetic factors responsible for them are existent in our herd and have appeared only when certain matings were made. The evidence against hereditary transmission is almost overwhelming, and may be briefly set forth as follows: (1) No other blind pigs have been farrowed in our herd since this herd was established twenty

years ago. (2) The three sires and the four dams of the forty-two defective pigs had apparently normal vision. (3) The three sires have produced only normal pigs when bred to other sows. (4) were from gilts unrelated to the gilt that farrowed the eyeless pigs in 1932, and their sire was of a different breed. (6) The only eyeless pigs produced in our herd have been from sows that were

Table 1

DATA PERTAINING TO THE PRODUCTION OF BLIND PIGS FROM NORMAL SOWS FED RATIONS DEFICIENT IN VITAMIN A

Dam No.	Sire Breed-No.	Date Litter of Pigs Farrowed	No. of Pigs in Litter	No. of Pigs Born Blind	No. of Normal Pigs	Kind of Ration Fed Dam of Litter	Other Defects in Litter of Pigs
38	Essex-2	3–29–32	11	11	None	Vitamin-A deficient**	Misplaced kidneys in 2 pigs
38	Duroc-3	8–19–32	4	None	4	Vitamin-A deficient plus green pasture	None
114	Duroc-5	3–20–33	8	None	8	Vitamin-A deficient plus 1% cod-liver oil	None
20	Duroc-5	3–27–33	9	None	9	Vitamin-A deficient plus 1% cod-liver oil	None
336	Duroc-14	6– 8–34	10	10	None	Vitamin-A deficient**	Subcutaneous cysts, cleft palates hare lip, misplaced kidneys, extra ear-like growths
187	Duroc-14	6– 8–34	14	14	None	Vitamin-A deficient**	Misplaced kidneys
336	Duroc-45	12–17–34	10	None	10	Vitamin-A deficient plus green pasture	None
187	Duroc-45	12–20–34	11	None	11	Vitamin-A deficient plus green pasture	None
49	Duroc-1	5–11–35	7	7	None	Vitamin-A deficient**	Harelip, cleft palates, misplaced kidneys, extra ear-like growth
46	Blind boar son of sow 187	5–11–35	11	None	11	Vitamin-A deficient plus green pasture	None
187	Blind boar son of sow 187	5–19–35	8	None	8	Vitamin-A deficient plus green pasture	None
12*	Blind boar son of sow 187	5–26–35	7	None	7	Vitamin-A deficient plus green pasture	None

* Blind gilt out of sow 187.
** Dam started on cod-liver oil on 30th day of gestation period.

The 1932 eyeless condition was duplicated exactly in 1934 and again in 1935, but only in connection with vitamin-A-free rations. (5) The two litters of defective pigs farrowed in June, 1934, practically depleted of vitamin A at the time of conception. (7) Definite and complete genetic tests were made in order to determine whether or not we were working with an hereditary

anomaly already in the stock of pigs we were using. These tests included the mating of the blind male from one of the 1934 litters of blind pigs (a) to a normal, unrelated gilt, (b) mating the blind male back to his dam, (c) mating the blind male to his blind full sister and litter-mate. From these three matings, 26 normal pigs and no abnormal pigs were farrowed.

As a matter of fact, it will be obvious to any one familiar with the principles of heredity, that there are only two hereditary mechanisms by which normal parents could produce blind offspring. The first possibility assumes that both parents were heterozygous for recessive factors responsible for blindness, in which case one fourth of the offspring on the average would be expected to be blind, just as in humans two brown-eyed parents may have some blue-eyed children. This possibility is ruled out by the first litter of eleven blind pigs, even without additional evidence that has since accumulated. There is only one chance in about four million of all the offspring in a litter of this size being recessive, an event, for all practical purposes, not so much more common than an all-trump hand in bridge, or the birth of human quintuplets. The second possibility is that the two normal parents carried complementary factors which when combined in the offspring produced these various eye and other defects in the same way that the crossing of two white-flowered sweet peas sometimes produces purple flowers in the first generation. Such a situation could easily result in blindness in all of the offspring, but this hypothesis is ruled out because the blind pigs themselves have completely failed to transmit their blindness to their offspring, even in very close matings, such as brother and sister and mother and son (see table 1).

These studies leave no reasonable doubt that a maternal deficiency of vitamin A will result in a variety of defects in the offspring, including blindness and even a failure of complete development of eye tissues, cleft palates, hare lip, and the arrested ascension of the embryo kidney. The question at once arises as to the relation of these results to various eye defects and weaknesses in the human race. It may be argued that there is a vast gap between pigs and people, but from the biological and nutritional standpoint, the differences are not so great as might appear at first glance. Both are omnivorous mammals with a relatively long gestation period.

It must not be forgotten, of course, that the nutritional conditions which brought about our litters of blind pigs are extreme and exaggerated. It would be almost impossible for an expectant mother to be as nearly depleted of vitamin A as were the animals in our experiments. On the other hand, vitamin-A deficiency is by no means uncommon in human diet—especially where the variety of food is limited. Furthermore, the instance of the one gilt that received a single dose of cod-liver oil two weeks before conception, and subsequently gave birth to pigs with eyes, but with a variety of defects including blindness, points to the fact that there are various degrees in which a lack or deficiency of vitamin A can affect eye development. Just as Dr. H. M. Taylor has recently discovered that some of the deafness among Southern children is due to quinine taken by the mother during pregnancy, so it may easily be that many of the eye weaknesses which we suffer today, are due to maternal vitamin-A deficiency. Perhaps we have been forcing our spinach on the wrong victims; it ought to be administered to the mothers instead of the children. In any case, it is obvious that until we have evidence to the contrary, we should insist on an abundance of vitamin A in the diet of the expectant mother in the early stages of pregnancy when so many of the vital organs of the embryo are being formed.

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Discussion. DR. WALTER B. LANCASTER: I should like to ask if any investigation was made to see whether blindness in humans is connected with a deficiency in vitamin A.

MR. HALE: You mean in the literature. There is nothing in the literature that I could find that would indicate that any observations have been made and conclusions drawn to that effect, but, on the contrary, there is nothing to show it was not. I do not think the subject has been studied from the naternal vitamin-A-deficiency standpoint. Most of what I was able to find relates from the date of birth instead of previous to birth.

DR. A. M. YUDKIN: I should like to state that anophthalmos, microphthalmos, and macrophthalmos, unilateral and bilateral, were observed in our rat colony previous to 1927. These ocular malformations were not found in subsequent litters of the same combination of parents when subjected to a similar environment and fed the same type of diet. The rations were adequate in maintaining normal growth and good health.

A similar observation was made in another well-known rat colony in this country. It is not unusual to find ocular deformities in other laboratory animals, particularly in the rabbit.

If sterility is associated with a vitamin-A deficiency, would you expect to have specimens for examination? Even though the diet may be lacking in vitamin A, would you not find other types of ectodermal disturbance?

I should like to see further observation made in his and other agricultural stations on pigs before concluding that the ocular changes are directly due to vitamin-A deficiency.

MR. HALE: In the four gilts I showed you in the graph we had a complete setup, two gilts receiving vitamin-A-deficient rations, the other two receiving the same rations plus one percent of cod-liver oil. Only the gilts receiving the cod-liver oil that furnished the vitamin A had perfectly normal pigs. We have duplicated the condition we observed in 1932, three different times with unrelated animals and have taken these animals and have proved to the geneticist and to anyone familiar with heredity that the eye anomaly was not due to heredity.

We have taken these deficiency rations and added cod-liver oil and have never been able to get these defects on such rations. We have produced forty-two blind pigs with these vitamin-A-deficient rations. We have produced these defective pigs by using two points

of technique that are of paramount importance. First, the mother must be depleted to a very low state in vitamin A before breeding. Second, the vitamin-A-deficient ration must be continued after the animal is bred until the stage of embryonic eye development has passed, and there is nothing in the literature that I can find to show that such tests have been made other than what I have read here today according to our method of procedure.

DR. FREDERICK H. VERHOEFF: I should like to ask if it ever failed when you tried to do that?

MR. HALE: Yes, it has, but it is hard to tell when these animals are depleted to the state where vitamin A is practically depleted out of the body. You have to observe that yourself and be enough of an animal husbandman to know the symptoms exhibited by those pigs with vitamin-A deficiency. I doubt if anyone who is not familiar with pigs showing vitamin-A deficiency could ever succeed, except through trial and error for a good many periods.

We succeeded the very first effort we made, after we selected young gilts the same age and weight of the first gilt. When we failed, it was with mature animals. We thought the one-hundred-and-sixty-day period on which we kept the first gilt was of some significance, but found it is not of any significance. The important feature is to deplete the animal to a very low state in vitamin A. We kept mature animals on a deficient ration for one hundred and sixty days and failed, but never have failed when we withheld breeding until the animals showed depletion, by these vitamin-A symptoms, to a very low state.

DR. THOMAS B. HOLLOWAY: I should like to know whether sufficient time has elapsed to determine whether these blind pigs represented a true case of anophthalmos or simply instances of excessive microphthalmos. In one slide shown the optic nerves entered the orbits.

MR. HALE: It is not a true anophthalmos. Only by microscopic examination would you know there was no anophthalmos. We have not gone very far with microscopic work yet.

DR. C. W. RUTHERFORD: What effects of these experiments were noted on the orbits and the extraocular muscles?

MR. HALE: We have not made those observations yet. We have these animals, however, in formalin, and we intend to make very extensive studies along that line.

DR. EDWARD JACKSON: Would it not be a fair supplementary experiment to subject an entirely different species and different family of animals, rats, to a similar vitamin-A-deficiency diet and see what the effect would be on them? Would that be in the same line of experiment?

MR. HALE: These experiments are only four years old and are so new that they are just in their infancy. There are so many angles to the question that studies will have to proceed for several years before we can get at this problem from all angles.

But if we should use rats (we are using rats now) and fail, you might ask yourself the question—Will we say the lack of vitamin C does not cause scurvy because we cannot give scurvy to a rat?

DR. LANCASTER: Has it been tried in poultry?

MR. HALE: No, not in poultry.