specific factor, such as the local formation of antibodies or local mobilization of antibodies which cooperates in the process. This question and many others are being investigated in pursuit of the observations already stated, which we believe offer a most promising and concrete introduction to an histology of immunity.

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Active and passive protein sensitization in utero.

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It seemed probable to one of us that protein sensitivity in certain cases of early infancy might have some relationship to prenatal conditions.

Time does not permit our going into a detailed discussion of our hypothesis, nor can we enter into the clinical considerations, nor historical background for our work. We would merely like to present certain investigations on guinea pigs, which may have a bearing on this problem.

There has been a small but clearly defined amount of work by Rosenau and Anderson,[1] Anderson,[2] Gay and Southard,[3] Wells,[4] and others, on the passive transfer of antibodies from mother to offspring.

In the study of 29 guinea pig families, in which the mothers had been injected with normal horse serum long before conception, we induced acute anaphylactic death in the offspring born of these mothers, by an injection of normal horse serum within the first twenty-four hours to a few days after birth, thus corroborating the work of others.

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1 Rosenau, M. J., and Anderson, J. F., *Hyg. Lab. Bull.*, 1906, xxix, 73.

2 Anderson, J. F., *J. Med. Res.*, 1906, x, 259.

3 Gay, F. P., and Southard, E. E., *J. Med. Res.*, 1907, xi, 143.

4 Wells, H. G., *J. Inf. Dis.*, 1911, ix, ii, 147.

We have also shown this passive sensitivity of the offspring to persist as a rule for 78 days, and in one instance, for 118 days. Thus for the present, we may assume that passive sensitization from mother to offspring generally lasts for about 2½ months, but may persist for even longer than 4 months.

Up to the present state of our investigation, we have shown this transfer to pass successively into the offspring of the second, third, and fourth litters, the mothers having received a single injection of horse serum before the first confinement.

In 15 families, in which the mothers were sensitized during pregnancy, the offspring, as in the former cases, showed sensitization at birth. We have not as yet demonstrated the influence that the antigen might have on the duration of sensitization in these offspring. This is under further consideration.

The foregoing experiments serve as a background for our present work. We believed, that if we could actively sensitize a mammal in the uterus of a mother, non-sensitive at the time of confinement, the experimental proof thus obtained, might be more in accord with the mechanism which may be present in certain of the remarkable instances of those infants born of non-sensitive mothers, who manifest profound anaphylactic symptoms when they ingest some protein food for the first time.

We have been unable to find any record in the literature of an attempt to clearly differentiate a passive transfer of antibodies from mother to offspring, from an active sensitization of a fetus *in utero*.

In order to accomplish our purpose, we attempted to so time the injections into the mother before confinement, as to obviate with certainty, the possibility for the establishment of antibodies before the birth of the offspring.

This was a difficult task, as one cannot easily time the date of parturition. It was therefore a question of guessing as nearly as possible, the end of a period of pregnancy, and thus make our injections within a few days before confinement. For example, we had 11 animals injected from 1 to 4 days, 18 that were injected between 6 and 10 days, and others which were injected a longer period before confinement.

It is obvious that when an animal was born within 1 to 4 days after the mother had been injected, no antibodies could have developed and been transferred to the offspring. However, in all instances, further evidence of a definitely non-sensitive state of

a family was obtained, by proving that either the mother or one of the offspring was not sensitized at the time of confinement. The remaining, or uninjected offspring, were then permitted to live for a month or more. This period of time, we believe, would suffice for the active development of antibodies—the direct result of contact of the fetus with the horse serum transferred from the mother's circulation through the placenta.

Not knowing the influence that an injection into the mother might have on the sucklings, we did not in every case, inject the mother after confinement, although in 10 families we have shown no evidence of transmission of antigen through the milk. This question is under further investigation.

The overwhelming number of these experiments resulted in an inability to produce this active sensitization *in utero*. These negative experiments total 26 families. In 8 families we obtained moderately suggestive results. In 3 families we obtained results that were fairly definite but not conclusive. In 1 family the results were very striking, but the period of injection prior to the confinement seemed too long to fit in with the criteria laid down above.

In view of the irrefutable fact, that antibodies pass through the placenta with regularity, the negative results that we obtained in the latter group of experiments, may be due to many factors, which at the present time cannot be answered. Among these considerations, there is the question of the length of time that it takes antigen to pass through the placenta, the question of whether this passage occurs in every instance, and the question of the ease with which the fetus is able to develop an active sensitization.

However, we believe that we have in two instances, definitely shown that a fetus can be actively sensitized *in utero,* and present the following two experiments as proof.

Mother 541, on 10/23/25, received a 10 cc. intravenous injection of horse serum. On 10/25/25, which was exactly two days after the injection of horse serum, this mother gave birth to two offspring. On 10/30/25, one of the offspring, five days after birth, or seven days after the mother had received her injection, was given an intravenous injection of 1 cc. horse serum. This animal remained perfectly normal. The second, or remaining offspring, on 11/20/25, was thirty-five days old, when it also received an intravenous injection of 1 cc. horse serum, and

promptly died in acute anaphylactic shock, presenting typically anaphylactic lungs.

In this instance, it seems clear, that the initial injection to the offspring, must have in reality been the second or toxic dose to the primary sensitizing dose it had received *in utero*. The negative reaction of the first offspring, in face of the overwhelming evidence of anaphylactic death, occurring in newly born guinea pigs of sensitized mothers, indicates very strongly that the sensitivity developed by the second offspring was that of an active production of antibodies.

Mother 310, on 5/19/25, received 2 cc. of horse serum intraperitoneally. On 5/22/25 (three days later), gave birth to one offspring. As long as fifteen days after the mother's first injection, *i. e.*, 6/5/25, we were fortunately able to show that this mother remained perfectly normal, after a 1 cc. intravenous injection of horse serum. The offspring was then permitted to live for twenty-eight days, and on 6/19/25, was given an intravenous injection of 1 cc. horse serum, and promptly died in acute anaphylactic shock. On this same day (6/19/25) the mother received her third injection of 1 cc. intravenously, and also promptly died in acute anaphylactic shock. This lends further evidence to the fact that on 6/5/25, the negative response of the mother to the second injection shows that she gave birth to her offspring before she was sensitized. (Three days as noted above is generally regarded as too short a time for the development of antibodies.)

These facts obtained in guinea pigs, we hope may suggest some possible explanation for certain instances of anaphylactic reactions in early childhood, when these individuals ingest some foreign protein for the first time. We are engaged in further studies on this entire problem.