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PRESIDENT'S ADDRESS.

DOES ANIMAL EXPERIMENTATION SHOW SIMILAR
CHANGES IN THE EAR OF MOTHER AND
FETUS AFTER THE INGESTION OF
QUININE BY THE MOTHER?

DR. HARRIS P. MOSHER, Boston.

I very greatly appreciate the high honor of being chosen President of this old and most distinguished Society.

For quite a few years, Dr. Marshall Taylor has been hammering away with bulldog tenacity accumulating clinical evidence that quinine taken by the mother can cause deafness in the child. I have been impressed, as many of you must have been, by the clinical data which he has assembled in support of his contention.

In looking for a subject to speak to you about today, not being by birth or training a physicist or a mathematician, I chose a subject which required humbler talents, namely: "Does animal experimentation show similar changes in the ear of mother and fetus after the ingestion of quinine by the mother?"

Accordingly, for the past year and a half I have been working at this question. Eleven adult pregnant guinea pigs have been given quinine in varying doses over varying periods, and 21 feti from these mothers examined; three pregnant pigs were given sodium salicylate and seven feti obtained for examination; one pregnant pig was given mapharsen and two feti obtained and examined.

Six adults were not given medication and were used for controls. In all, 54 animals were studied.

The subject of the paper I have just given. The paper itself consists of the presentation of the findings in 54 animals. I shall deal only with the subject of hemorrhage and only with the findings in the guinea pig. By inference I shall imply that the findings would probably be similar in man

were like experimental conditions possible. I shall disappoint Dr. Taylor somewhat because I have not proven that any of these animals were made deaf. To do this would take another year, at least. I have been working on this subject only a little over a year. To prove what he wishes to have proven and which I think will in time be proven would mean that instead of sacrificing the mother and fetus, as I did, the fetus would be allowed to be born, to live awhile, have its hearing tested by modern methods, and then be killed. Dr. Lurie, who is working at this type of experimentation, will probably have something to say on this subject when sufficient time has elapsed. As far as I am concerned, Dr. Taylor will have to be satisfied with a lesser favor; namely, I can show that quinine and salicylic acid produce similar changes in the internal ear of mother and fetus, the changes being more marked in the fetus. The initial effect of these two drugs given either in overwhelming doses, or in doses over protracted periods until the animal becomes toxic, is hemorrhage. This may occur in any part of the cochlea, about the basilar artery and even in the medulla.

The frequency with which hemorrhages in the cochlea are found with and without medication speaks for the ease with which they are produced and is the worst feature about them. Only when repeated to the point of the formation of fibrous tissue in places vital to hearing, to the strangulation of ganglion cells, or to the obliteration of a fundamental portion of the blood supply, do they become of importance as a cause of loss of hearing.

ORDER.

The order of the paper is as follows: The method of examination; the ear findings after the giving of quinine to animals, as reported in the literature; a statement of the findings in the animals used in the investigation; the blood supply of the cochlea; summary and conclusions.

Dr. Lurie knows more about the finer anatomy of the internal ear than I do, and more than a good many of the rest of us, due to his work with Prof. Davis and the phy-

siologists collaborating with him. I asked Dr. Lurie to assume the role of a doubting Thomas in reviewing my findings. He has played his part most faithfully, but always kindly. I was especially anxious not to overdraw my conclusions, and equally anxious not to make false observations; therefore, if I am wrong, he is wrong. In this case, therefore, two shoulders carry the burden.

THE METHOD OF EXAMINATION.

The X-ray was used to determine pregnancy as well as the imminence of delivery. Most of the feti were obtained by abdominal section at the middle of pregnancy or near term. When the X-ray showed that one fetal head was at the brim of the pelvis, the mother was sacrificed.

The first pigs were given quinine by injection into the muscles of the abdominal wall. This produced such cruel sloughs that mouth feeding was substituted, at first by dropper, then by quinine in capsule. This method, which was suggested by Dr. Wherry, has proven most satisfactory.

The gestation time of a guinea pig is about 72 days. In order not to have the delivery get ahead of us and occur on a Saturday or holiday, or at night, and ruin the specimens, around the fourth or fifth week, when the X-ray showed that one fetal head was well engaged in the brim of the pelvis, the animal was chloroformed and the feti removed by section.

In the beginning, when the quinine was given subcutaneously, a number of pigs aborted. This has not been so frequent with mouth feeding. It has not happened when the animal was overwhelmed with doses of quinine every half hour for four or five hours, until it was sick unto death.

There is no stated group of symptoms in the animals overwhelmed by half-hour doses until they become toxic. They show weaknesses in their hind legs, stagger aimlessly about, develop convulsions, and finally usually die in one.

Those of you who have done any of this work know that the preparation of the specimens is long and often surrounded with disappointment. As the conspicuous action of quinine

on the adult and fetal internal ear is hemorrhage, I did not have the preserving fluid injected by way of the common carotid artery, but relied on killing the mother just before delivery, removing the feti by section, opening the bulla in order to bring the preserving fluid in contact with the cochlea and getting the whole specimen into the preserving solution with the utmost speed. In spite of these precautions, post-mortem degeneration was always a bugbear.

Fortunately, I was not studying the organ of Corti particularly, or looking for nerve degeneration, but was investigating only blood vessel changes and hemorrhage.

FINDINGS REPORTED IN THE LITERATURE.

Blood in the cochlea is a very common occurrence. It varies from what I believe is a physiological amount; that is, a few corpuscles or a thin line of corpuscles, one or two deep at the bottom of the basal whorl, to an amount of blood which can be classed as a hemorrhage. Investigators, working on the inner ear, generally dismiss a small amount of blood as an artefact, saying that it reaches the cochlea from the cranial cavity by way of the cochlea aqueduct. Other observers feel that the hemorrhages are similar to those in the human baby at birth and are due to asphyxia accompanying delivery, while others maintain that asphyxia is the cause, but think it is produced by the lethal dose of chloroform used to kill the animal.

It has been proven on adult animals that the ingestion of certain drugs, notably quinine and salicylic acid, is associated with hemorrhages in the cochlea. The investigators who have reported these findings have generally held that the hemorrhages are caused by the convulsions which the toxic action of the drugs produce; furthermore, after the giving of quinine, changes in the ganglion cells and in the organ of Corti have been found in the adult pig. Dr. Lurie has repeated the quinine experiments on the adult pig and found all the changes just mentioned. Recently Covell reported changes in the mitochondria of the ganglion cells of the auditory nerve of a pig whose mother had been given quinine.

Quinine has been found in mother's milk and in the placenta. This is as one would expect. One would expect, also, similar effects of quinine on mother and fetus.

SUMMARY OF MATERIAL.

Eleven adults, 23 feti: Mother given quinine.

Three adults, seven feti: Mother given salicylate of soda.

One adult, one fetus: Mother given mapharsen.

One young adult: Experimental fracture of skull; no quinine.

One young adult: Strangled; no quinine.

Six adults: No quinine.

Total feti, 31; total adults, 23. Total animals, 54.

Fifty-four animals in all were put through. In at least half of these the posterior part of the medulla and the cerebellum were removed and sectioned with the temporal bones. Both temporal bones were mounted on one slide. The sections averaged 14-16 microns. Forty to 50 sections were cut from each temporal bone and were mounted and studied in series.

DOSAGE.

The extremes of doses of quinine given were 6 cc. in two days and 92 gr. in 120 days. The average doses for the rest of the animals were around 20 gr.

The following four pigs show the findings in the minimum and maximum doses:

No. 45: Nine days old; 6 cc., two days. Findings: Hemorrhage about the VIIIth nerve. Hemorrhage into bone marrow.

No. 81: Adult female; 61 gr., four and one-half months. Findings: Hemorrhage into the scala tympani, basal whorl.

No. 242: Fetus near term. Mother given 75 gr. quinine in 115 days. Findings: Slight hemorrhage into the scala tympani; no dilated vessels.

No. 78: Adult female (aborted twice; feti too young for study); 92 gr. quinine, 120 days. Findings: Slight hemorrhage in the scala tympani.