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Neonatal Hydrocephalus in the Offspring of Rats Fed during Pregnancy Non-toxic Amounts of Tellurium* **

By

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With 7 Figures in the Text

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Tellurium has metallic properties and with its specific gravity of 6.2 can to certain extent be counted to the heavy metals. However, its behavior in animals is such that it can be called the "anarchist" among them. So, for instance, tellurium has complete disregard for the blood-brain barrier and for the cellular membranes as well, and, since, in addition, it has the tendency to accumulate in the nerve cell bodies, the brain gradually takes on a dark grey, almost black, color in prolonged administration (Jahnel, Page and Müller 1932). Curiously enough tellurium does not traverse the brain-cerebrospinal fluid barrier. All these extravagances and many others (Pentschew 1934, 1958; Pentschew, Ebner, Kovatch 1962), however, are revealed only by treatment with 2—5 simultaneous intramuscular injections of the water-insoluble metallic tellurium suspended in olive oil. Thereby apparently water soluble tellurium ions are continously released from these tellurium deposits, thus meeting the prerequisites for a real chronic poisoning. The amount of the released ions pro die are apparently very small since water soluble tellurium compounds proved to be extremely toxic (Hansen 1856; Beyer 1895; Pohl 1926; Pentschew and Kassowitz 1932). This is in contrast with the observation that animals with almost "black" brains show no appreciable neurological symptoms and can be kept in good condition for several years.

Effect of tellurium on the fetal brain

Pilot experiments on three rabbits injected with metallic tellurium during pregnancy showed interesting results. Twelve of the 16 surviving offspring had a definite disturbance of equilibrium with ataxia for about three months. The neurological symptoms slowly subsided and later disappeared, except for one animal. A morphological substrate for the neurological disorder was not found. The cumbersome parenteral administration of tellurium hindered a more extensive investigation of this disorder. The situation changed when we found that *peroral* administration of metallic tellurium is an excellent substitute for the parenteral application. This new method is easy and facilitates the use of animals

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in great numbers. We chose the rat, since it readily accepted the diet containing tellurium.

In the course of testing the toxicity of the perorally administered tellurium on more than hundred adult rats (Long-Evans strain) we found that a diet containing telluium (1,250 to 2,500 parts pro million parts food, ground laboratory chow) fed during pregnancy leads to hydrocephalus in the offspring. With 2,500 p.p.m. the yield was 100 per cent, with 1,250 p.p.m. it varied between 60 per cent to 90 per cent. In certain colonies even 500 p.p.m. tellurium were effective although the yield was lower and only a part of the litter was affected. When the optimal dose, i.e. 2,500 p.p.m. was used the dams were put on normal diet 3—5 days before the expected delivery to avoid abortions. When the content of tellurium in the diet was lower than 2,500 p.p.m. the dams were put on normal diet only after birth. They tolerated the diets containing tellurium well and behaved normally. The delivery occurred on schedule.

Material and methods

The brains of approximately 50 newborn hydrocephalic animals ranging in age from 1 to 28 days were examined in serial sections in three different planes (coronal, horizontal and sagittal). The heads of animals no older than 5 days were embedded in paraffin in toto after fixation in formalin. In older animals the embedding was preceded by decalcification of the skull. Only in a few cases was it possible to remove the brain without distorting its structure. The 18 μ sections were stained with cresyl echt violet whereby the various extracerebral organs of the head showed metachromasia in all imaginable shades. The viscera were stained with H.E. For the demonstration of the hydrocephalus in vivo we used ventriculography, which was easily performed, and also injection of thorotrast through the thin wall of the skull. The outflow through another inserted needle balanced the intracranial pressure.

Results

With this method we have produced hydrocephalus in more than 200 offspring of mothers fed non toxic amounts of tellurium. The newborn animals appeared normal except for being smaller than the controls. The hydrocephalus started immediately after birth and around the third week reached its greatest dimensions (Fig. 1). X-ray photograms of the skull completed the picture (Fig. 2). The hydrocephalus could be demonstrated also by insufflation of air and by injection of thorotrast (Figs. 3 and 4). The neurological signs consisting of moderate impairment of the gait were amazingly inconspicuous despite destruction of the telencephalon, and in late stages of development of great parts of the diencephalon. A sudden paralysis of the limbs and turning on the back was the sign of impending death, resulting obviously from the excessive intracranial pressure. Lethality was about 99%, the longest survival period being one month.

The hydrocephalus was characterized by dilatation of the entire ventricle system (Fig. 5). In the incipient stages it was most prominent in the lateral ventricles and could be established in the majority of the

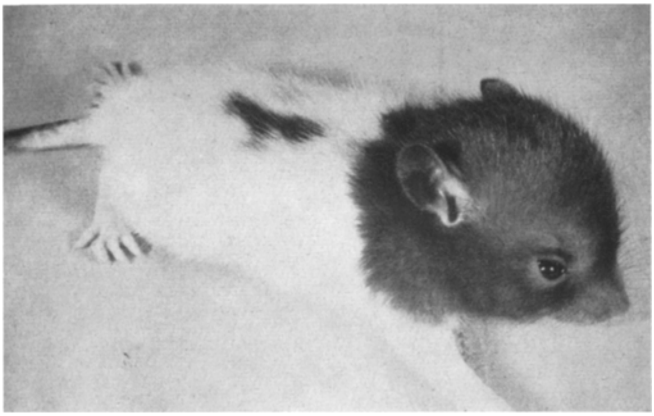

Fig. 1. Hydrocephalic rat, 18 days old

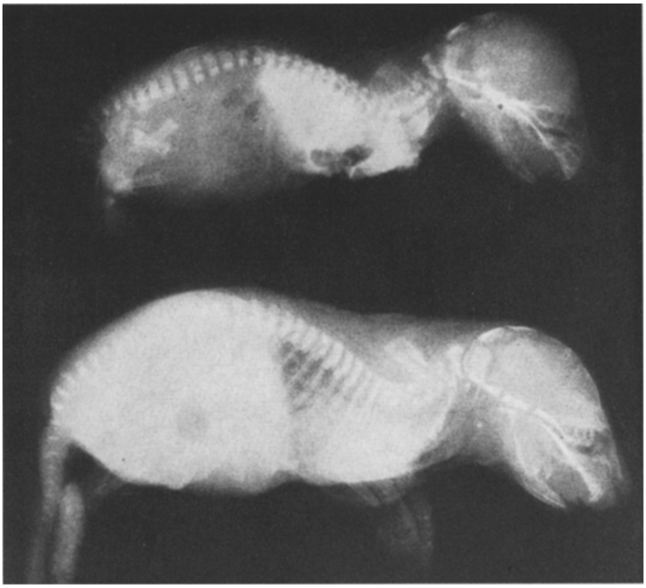

Fig. 2. Hydrocephalic rat, 3 days old (above), with control animal of the same age (below). Note the difference in the configuration of the skull and of the size of the body. The difference of the size was in this case extreme. It varies and is to a great extent related to the dosis of tellurium

animals as early as a couple of hours after birth. As the process progressed dilatation of the aqueduct and of the fourth ventricle became more prominent. No obstruction of the communicating ventricular channels and of the drainage system was found. The arachnoidea looked normal. There were no malformations. In the early stages (1—2 days) there was no disintegration of the tissue. Later, serous imbibition and

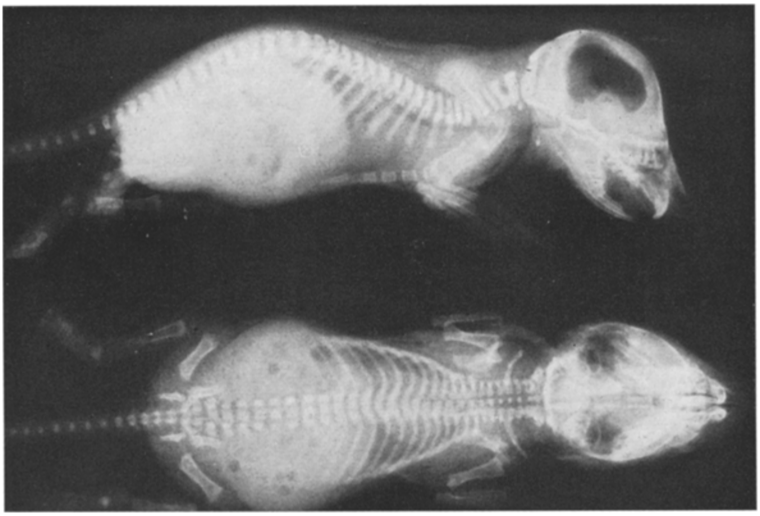

Fig. 3. The hydrocephalus in this 7 days old rat is demonstrated by insufflation of air

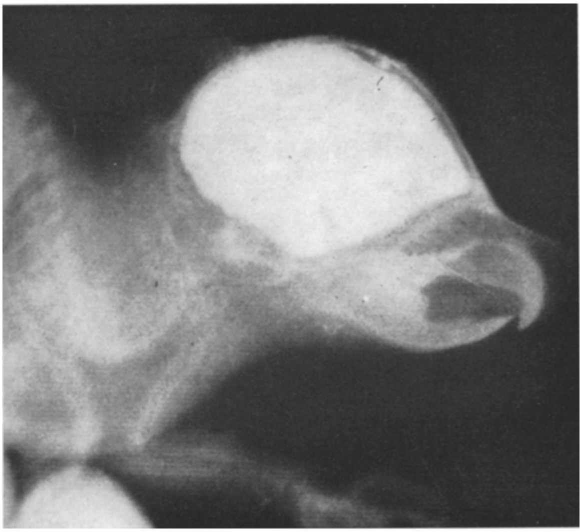

Fig. 4. 18 days old rat. The hydrocephalus here is demonstrated by thorotrast

liquifaction of the tissue with formation of cavities developed (Fig. 6). The white matter was less resistent than the grey matter which often framed the cavities. Almost complete disappearance of the telencephalon

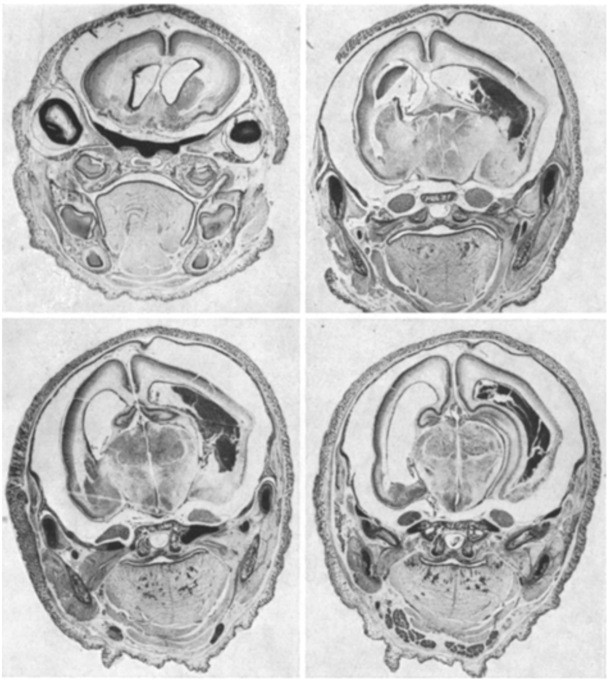

Fig. 5. Coronal sections of the skull at different levels in a 2 days old rat with hydrocephalus of the lateral ventricles. Early hemocephalus, one-sided, possibly precipitated by the procedure of sacrificing. The third ventricle and the aqueduct patent but not enlarged. In later stages these ventricles and the fourth ventricle are often significantly enlarged. The enlargement of the subarachnoidal spaces is artefactitious, due to the shrinkage of the brain during embedding. Nissl stain ×3

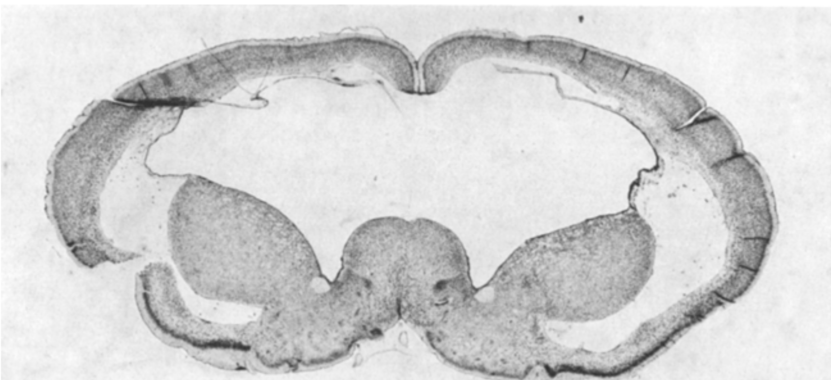

Fig. 6. 21 days old hydrocephalic rat. Section at the level of the oral striatum. Septum and corpus callosum have disappeared. The hydrocephalus outlined by the resistent ependymal cover. Liquifaction of the white matter with formation of cavities not directly related to the hydrocephalus. Nissl stain ×8. AFIP Neg. 64-2715

and in some animals also of the diencephalon in advanced stages (2—3 weeks) was the rule. The mesencephalon and the metencephalon were always preserved. The reparative processes were confined to appearance of gitter cells.

Hemorrhage was a complicating factor and occurred in two forms. The first was a hemorrhage "by diffusion" obviously related to the breakdown of the blood-cerebrospinal fluid barrier, and did not contribute essentially to the increase of the intracranial pressure. It could be observed as early as a few hours after birth and was often one sided. The second, late form, was a hemorrhage "per rhexin" due to erosion of blood vessels. It was often the immediate cause of death.

Discussion

The pathogenesis of the tellurium hydrocephalus is obscure since no obstructions within the ventricle system and no malformations of the brain were found. It should be added that adult rats treated with tellurium never develop hydrocephalus. Our assumption is that the hydrocephalus is due to a pathologically increased permeability of the blood-cerebrospinal fluid barrier. This results in an excessive transudation of blood fluid into the ventricle system, upsetting the balance between inflow and outflow of the cerebrospinal fluid. The term "transudation" indicative of a passive process has been chosen instead of "secretion" which is an active, energy consuming process.

A direct effect of tellurium on the epithelial cover of the choroid plexus as cause of the breakdown of the blood-cerebrospinal fluid barrier is improbable, since in many previous investigations we were unable to demonstrate that this heavy metal permeates the placentar barrier in significant amounts. We are, therefore, more inclined to think that it produces in the mother a metabolic disorder resulting in deficiency of some specific factor necessary for the full maturation of the blood-cerebrospinal fluid barrier. This immaturity is probably at a functional level, since changes found sometimes in the epithelial cover of the choroid plexus were questionable. The immaturity concept is supported by the fact that the offspring of the mothers treated with tellurium were smaller in size than the controls. That tellurium inhibits the growth was shown in previous unpublished experiments, whereby newborn guinea pigs treated with tellurium by intramuscular injections, showed significant retardation of their growth. Six months after discontinuing of the administration of tellurium, at the age of 3 months, the treated animals, however, caught up in size with the control animals.

The development of the hydrocephalus after birth would suggest a dramatic change of the activity of the blood-cerebrospinal fluid barrier post partum as a physiological phenomenon. However, hydrocephalus may develop during the fetal period (Fig. 7) when the amount of tellurium in the diet exceeds 2,500 parts pro 1,000,000 parts or if the tellurium diet is not suspended a few days before delivery. In such cases the latter is delayed, the fetuses are abnormally large, and as result of this anomally the dams die during or soon after the delivery. The problem of the *prenatal* hydrocephalus internus produced by tellurium and its relation to its postnatal variety is not investigated sufficiently to allow further conclusions. It appears that there are transitions between these two conditions. This is demonstrated also by the fact that the severity of the hydrocephalus does not correspond always to the age of the offspring so that a one day old newborn can show more pronounced hydrocephalus than, for instance, a 3 days old one.

Fig. 7. *Prenatal* hydrocephalus. Delivery delayed about 3—4 days. All the offspring were larger than the controls

Experimental hydrocephalus internus has been produced in the young born to rabbits which had been maintained on a vitamin-A deficient diet for a long period (14—38 weeks) before mating (MILLEN, WOOLLAM, and LAMMING 1953; MILLEN and WOOLLAM 1956). At three to five weeks of age these young showed head retraction, incoordination and paralysis. On radiological examination the skulls showed appearances suggestive of hydrocephalus and this was confirmed at autopsy when gross dilatation of the lateral and third ventricles was discovered. ROKKONES (1955) found that when female rats were fed from weaning on a diet low in vitamin-A and mated at about 6 months the young appeared normal at birth. However, when the mothers were maintained on the same diet for a further period many of the young in later pregnancies were hydrocephalic.

Considered as a whole, observations with hypovitaminosis and with hypervitaminosis-A (MILLEN, WOOLLAM, and LAMMING 1954) suggest that this vitamin is closely linked to the cerebrospinal fluid. According to MILLEN and WOOLLAM (1958) a fine adjustment appears to exist in the amount of the vitamin required to maintain the homeostasis of the fluid, and any alteration of the balance between production and absorption will produce disturbances in the cerebrospinal fluid.

The most striking resemblance to our findings is shown by the hydrocephalus of the offspring of rats depleted of vitamin B_{12} (O'Dell, Whitley and Hogan 1951, Newberne and O'Dell 1961). It is too early to draw conclusions concerning a possible common pathogenetic factor of the hydrocephalus related to vitamin imbalance and that caused by tellurium since the metabolic disorder produced by this heavy metal is still unknown. It appears, however, that none of the hydrocephalus produced by various vitamin deficiencies, except possibly the vitamin B_{12} deficiency, has the pernicious character of the hydrocephalus caused by tellurium. From this we conclude that whereas in the avitaminotic hydrocephalus we are dealing merely with a *dysfunction* of the blood-cerebrospinal fluid barrier, in the latter we are witnessing a complete *breakdown* of this barrier.

Summary

Because of the consistency with which a rapidly progressing hydrocephalus internus can be produced in the offspring of rats fed on a diet containing tellurium during pregnancy, this heavy metal appears to be an easy to handle and promising tool for the investigation of certain aspects of the congenital non-obstructive hydrocephalus internus.

Zusammenfassung

Nachkommen von Ratten, die während der Tragzeit mit geringen, kaum toxisch wirkenden Mengen von Tellur gefüttert wurden, entwickelten einen rasch progredienten Hydrocephalus internus. Tellur erscheint daher als einfaches und vielversprechendes Mittel zur Untersuchung kongenitaler nicht obstruktiver Hydrocephalus-Syndrome.

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