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# EXPERIMENTAL HYDROCEPHALUS

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In striving for a better understanding of the etiology and treatment of hydrocephalus, researchers have discovered and developed numerous experimental methods for afflicting this disease entity upon laboratory subjects. While Pudenz, Russell, and Agnew (1960) have presented an excellent and comprehensive review of the literature, a concise and orderly description of the development, consistency, and underlying pathophysiology of the most potential of these methods will assist the worker in his choice of procedure.

## THOSE APPROACHES INITIATED BEFORE BIRTH OF THE SUBJECT

### *Maternal folic acid and vitamin B 12 deficiency*

Richardson and Hogan in 1946 noted hydrocephalus in 1.7 per cent of the offspring of female *rats* which had received a diet lacking ascorbic acid and certain of the B-complex vitamins. These results soon were duplicated in an unrelated colony of rats (Richardson and DeMottier, 1947). O'Dell, Whitley, and Hogan (1948) suggested that the critical vitamin was folic acid. They could decrease the incidence by adding folic acid to the diet, and later obtained a 20 per cent incidence of hydrocephalus by adding to the diet a folic acid antagonist, crude methylfolic acid (Hogan, O'Dell, and Whitley, 1950).

They used two experimental diets: one with casein as the source of protein and the other with soybean oil meal as the protein source. A much higher incidence of hydrocephalus was noted among the first few litters of the mothers on the soybean oil meal diet, alerting them to another possible factor. This second factor was vitamin B 12 (Richardson, 1951; O'Dell, Whitley, and Hogan, 1951). Folic acid in the absence of B 12 would *not* prevent the abnormality, but it was not determined whether an adequate B 12 level in the absence of folic acid would prevent hydrocephalus.

B 12 treatment of the offspring failed to cure the hydrocephalus. Maternal B 12 administration indicated that irreversible changes occurred about the twelfth to fourteenth day of gestation (O'Dell, Whitley, and Hogan, 1951). In addition to hydrocephalus and high mortality, occasional cases of spina bifida, cranium bifidum, edema, anophthalmia or microphthalmia, hare lip, cleft palate, and short lower mandible were noted. Eye abnormalities were often present with hydrocephalus. The hydrocephalus appeared at birth or within three weeks, and the early mortality was high. Richardson (1951) maintained two hydrocephalics on a normal diet, mated them, and obtained normal offspring.

Overholser, *et al,* (1954) observed distended lateral and third ventricles in these hydrocephalic rats. The cerebral aqueduct was either completely closed or round in shape and smaller in size, as compared to the relatively large and irregularly shaped aqueduct in normal brains. In the roof of the posterior part of the third ventricle and the anterior portion of the cerebral aqueduct, a group of high columnar ependymal cells is normally present. In hydrocephalic brains, this group of cells is either partially or completely missing. These abnormal changes were not detected before the eighteenth day of gestation and were often present in a much milder form in many of the brains from litter mates of hydrocephalic animals.

Newberne and O'Dell (1958) reported an increased lipid content in the ependymal cells and choroid plexus, as well as an increased number of periaqueductal cells per unit area in hydrocephalic brains. They later demonstrated retarded development in lung, kidney, and bone, as well as irreversible degenerative brain changes and an increased number of mitotic figures in the ependyma of deficient brains (Newberne and O'Dell, 1959). Two explanations for the hydrocephalus were offered: The increased ependymal fat decreased absorption of cerebrospinal fluid, and a metabolic block led to aqueductal stenosis.

### *Maternal vitamin A deficiency*

There are many reports establishing the relationship of vitamin A deficiency and increased cerebrospinal fluid pressure. Especially interesting are those reports in which hydrocephalus appears among offspring of vitamin A deficient mothers.

In 1955 Rokkones noticed the occurrence of hydrocephalus among offspring of female *rats* on fat deficient diets. He reported an incidence of 100 per cent and eventually demonstrated that a maternal vitamin A deficiency was the apparent cause.

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Hydrocephalus among the offspring of vitamin A deficient *rabbits* was first reported in 1953 (Millen, Woollam, and Lamming) and a year later incidences of 74 and 92 per cent were reported (Lamming, *et al,* 1954; Millen, Woollam, and Lamming, 1954). Hydrocephalus and signs of increased intracranial pressure were usually present at birth.

Millen and Woollam (1956) demonstrated a direct correlation between the duration of the maternal vitamin A deficiency and the incidence of hydrocephalus. Obtaining an incidence of 58 per cent from mothers maintained on the deficient diet for 24-28 weeks, they also detected elevated cerebrospinal fluid pressures when no gross hydrocephalus was evident. Experiments with *chickens* confirmed the increase in cerebrospinal fluid pressure with the progression of the deficiency (Woollam and Millen, 1955, 1956). Administration of vitamin A to the hydrocephalic rabbits produced a pressure fall to normal levels after three to four weeks of treatment. (Millen and Dickson, 1956, 1957; Millen, 1956). Many lived a year or longer with vitamin A treatment.

There was usually marked dilatation of the first three ventricles with little or no aqueductal stenosis. Concluding that proper vitamin A levels are a prerequisite for normal functioning of the choroid plexuses, Millen and Dickson (1957) suggested that the hydrocephalus resulted from an increase in cerebrospinal fluid production. This was supported by the recent work of Witzel and Hunt (1962), who subjected the choroid plexuses of vitamin A deficient hydrocephalic rabbits to light and electron microscopy. Their studies indicated that the basic defect may be a weakening of the endothelial integrity of the capillaries in the choroid plexus, allowing excessive water and electrolytes to escape into the ventricular system.

It is interesting that signs of increased cerebrospinal fluid pressure have been noted in infants maintained on vitamin A deficient diets (Cornfield and Cooke, 1952; Bass and Caplan, 1955), as well as in an infant and dogs which had received excessive doses of vitamin A (Marie and See, 1954). It appears that the choroid plexus is very sensitive to gross alterations in vitamin A levels and responds with overproduction of cerebrospinal fluid (Millen and Dickson, 1957).

*Maternal metabolic poisons*

Gillman, Gilbert, and Gillman (1948) detected hydrocephalus and other defects in *rats* born to mothers injected with trypan blue before and during pregnancy. The incidence of hydrocephalus was 7.3 per cent of the total number of offspring or 38 per cent of the abnormal offspring. In about one-half of these cases, hydrocephalus occurred as an isolated defect, while in the other half it was associated with a large range of defects, including spina bifida, eye and ear defects, and dislocations of the hip, knee, and arm. However, there was no constant occurrence with any one anomaly. The seventh and eighth days of gestation apparently were the most critical time for the production of anomalies. Hydrocephalus usually was detected at birth, and its severity varied greatly. They noted a bulging cranium, dilated lateral ventricles, and a communicating ventricular system. The specific mechanism was not demonstrated.

In a larger series (Gillman, *et al,* 1951), hydrocephalus appeared among 12 per cent of the offspring. No abnormal features among three litters born to hydrocephalic parents were described, but the mortality of the newborn was 100 per cent.

*Maternal irradiation*

Irradiation of pregnant albino *rats* often produces anomalies in the offspring. Although diverse skeletal and nervous system defects usually are obtained, the specific type of defect depends to a great extent on the timing and dosage of the maternal irradiation. Job, Leibold, and Fitzmaurice (1935) reported 50.5 per cent abnormal offspring born to mothers irradiated on the eighth to eleventh days of pregnancy. Thirty per cent of the abnormal animals, or 15.5 per cent of the total, were hydrocephalic. Another similar group produced 18.6 per cent hydrocephalic offspring. The ninth day of gestation was the most critical period for the production of hydrocephalus.

Hicks (1952) noted that offspring born to female rats irradiated on the ninth and tenth days of gestation were characterized by "a deficient cerebral cortex, dilated cerebral ventricles ('hydrocephalus'), and a deficient or nearly absent hippocampal formation." He noted also that the nine-day, and some of the ten-day, animals did not survive. A year later Hicks (1953) described two associated deformities following maternal irradiation on the eleventh day of pregnancy: hydrocephalus and a narrow aqueduct. This proved to be an inconstant relationship, not cause and effect (Hicks, 1958). There was no intrinsic malformation of the aqueduct other than its small size—the stenosed portion was the proximal part of the iter from the third ventricle. Diverse skeletal defects often were obtained, but there was no constant relation to the hydrocephalus (Hicks, 1953).

Hicks noted that hydrocephalus usually occurred in the earlier phases of the 18-26 somite period. He concluded: "It seems that a thin cerebral mantle, excess fluid and absent skull vault are concomitant expressions of the very complex development that characterizes the effects of radiation here" (Hicks, 1958).

*Genetic influence*

Spontaneous hydrocephalus in *mice* has been studied extensively with four types genetically delineated: congenital hydrocephalus, hydrocephalus-1, hydrocephalus-2, and hydrocephalus-3. In each case the mode of inheritance was through a recessive gene (Carton, *et al,* 1956).

Congenital hydrocephalus was lethal at birth, and no milder degrees of anomaly were described (Grüneberg, 1943). The lateral ventricles were dilated, and there was no aqueductal blockage. Grüneberg believed the hydrocephalus was secondary to a defect in chondrification at the base of the skull, leading to a shortening of the basicranium and a resultant obstructive hydro-

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