

**PREVENTION OF CEREBRAL PALSY**  
**A RESEARCH STATUS REPORT**



**UCP Research and Educational Foundation**  
**1660 L Street, N.W., Suite 700**  
**Washington, D.C. 20036**

**June 2002**

## **THE UCP RESEARCH AND EDUCATIONAL FOUNDATION'S RESEARCH PROGRAM**

### **SUMMARY: PREVENTION RESEARCH**

- Cerebral palsy is a non-progressive disorder of the motor (muscle) control areas of the developing brain.
- There are 550,000 persons in the USA with cerebral palsy; the number of new cases per year has increased 25% during the past decade; now 9,750 new cases/year
- 70% of cerebral palsy occurs prior to birth (prenatal); 20% occurs in the birthing period (perinatal); 10% occurs during the first two years of life (postnatal).

#### **THE TARGETS OF THE FOUNDATION'S PREVENTION RESEARCH PROGRAM ARE:**

##### **PRENATAL BRAIN DAMAGE**

- Impaired migration of new brain cells to their destination in the developing brain is an important cause of cerebral palsy; major risk factors include infection, toxins, drugs and radiation exposure.
- Poor myelination (insulation) of brain nerve cell fibers is an important cause of cerebral palsy; a major factor is hemorrhage in the developing brain.
- Prematurity and low birth weight are major risk factors for cerebral palsy. Low grade infection of the mother's urinary-genital tract is a very common cause and is receiving priority research attention.
- The presence of multiple fetuses is an increasing reason for the occurrence of prematurity and developmental delay of the infant.

##### **PERINATAL BRAIN DAMAGE**

- Increased pressure on the infant brain during delivery, impaired circulation to the fetal brain, and poor respiration can result in brain cell death and are potential causes of cerebral palsy.
- A significant proportion of already existing prenatal brain damage is first recognized after delivery, but erroneously assigned to events in the perinatal period.
- Low birth weight is a major risk factor for developmental brain damage. Survival of very low birth weight infants is a reason for the increased occurrence of cerebral palsy. This relationship is receiving focused research attention.
- Improved neuroprotection of the threatened brain is also a principle research objective.

##### **POSTNATAL BRAIN DAMAGE**

- Physical trauma, infection, respiratory distress and cerebrovascular disorders are the most common causes of postnatal damage of the developing brain.
- Prevention of the complications associated with the disabilities resulting from cerebral palsy is of major importance to quality of life. This is an important Foundation research objective.

## **THE UCP RESEARCH AND EDUCATIONAL FOUNDATION'S RESEARCH PROGRAM**

Cerebral palsy is a disorder of the motor (muscle) control areas of the developing brain, injury to which occurred in intrauterine life thru the second year of postnatal life. The brain injury is a one-time event, although several different events can occur; each injury is non-progressive. The brain injury results in dysfunctions of muscle coordination often causing muscle spasticity, muscle weakness and/or abnormal body movements (e.g. athetosis); these can change over time. Cerebral palsy is not a genetic disorder although it can sometimes “run in families”; this is probably due to a genetic susceptibility to an environmental factor or to the continuing presence in or near the family of an environmental risk factor. Cerebral palsy can be associated with other damage to the brain resulting in epilepsy, a visual or hearing disorder, mental retardation or a learning disability.

There are 550,000 persons in the USA with disabilities due to cerebral palsy. The number is gradually increasing because of the growing number of new cases and the lengthened life expectancy of persons with cerebral palsy. There are now approximately 9,750 new cases of cerebral palsy occurring each year. The number of new cases has increased from 1.5-1.8 new cases per 1000 live births in 1990 to 2.0-2.5 new cases per 1000 live births in 2000; a 25% increase. Cerebral palsy is the second most common disorder of the developing brain, exceeded only by mental retardation.

The overall objectives of the Foundation’s research program are (1) the prevention of cerebral palsy (damage to that part of the developing brain controlling muscle coordination) and (2) the development of more effective methods for diminishing disability in order to improve quality of life.

### **PREVENTION RESEARCH**

Prevention of damage to the developing brain is a major goal of the Research Foundation’s program. Until recently, cerebral palsy (CP) was a “wastebasket” diagnosis describing the symptoms resulting from unspecified damage to the muscle control systems of the developing brain. However, in recent years the characteristics of the several different types of CP have been identified and have provided information about the specific brain pathologies that result in the different clinical manifestations of CP. Understanding the pathology supplies the research leads that help to identify the several possible causes; knowing the causes provides the insights needed for developing interventions to prevent damage to the developing brain. *The brain damage that occurs is a result of either (1) disturbance of brain cell migration, (2) poor myelination (insulation) of developing nerve cell fibers, (3) the death of brain cells, or (4) non-functional or inappropriate connections (synapses) between brain cells.*

At different times in fetal and infant development, specific areas of the brain are more vulnerable to damage. We now know that:

- 70% of developmental brain damage occurs prior to birth, primarily in the second and third trimesters of pregnancy (prenatal).
- 20% occurs in the birthing period (perinatal).
- 10% occurs during the first two years of life (postnatal).

The causes of CP can be very different in each of these developmental periods, as is the susceptibility to injury of specific areas of the developing brain.

### **PRENATAL BRAIN DAMAGE**

In the past, RH blood type incompatibility between the mother and fetus and the occurrence of German measles during pregnancy were important prenatal causes of cerebral palsy. Both are now preventable due to the development of vaccines; the development of each received financial support from the UCP Foundation. At this time, the principle causes of damage to the prenatal brain are disturbances to the *migration* of embryonic cells that form the brain and *injury* to the process that provides the insulation (myelination) surrounding nerve cell fibers (axons) originating in brain cells. Damage to the nerve cell body can also occur, but this is more common in the perinatal and postnatal periods.

### **Disturbance of Brain Cell Migration**

The brain begins as one end of a hollow tube, one layer thick. In the first weeks of fetal life, the single layer of cells (embryonic stem cells) begins to divide at the rate of 250,000 cells per minute and embryonic nerve cells travel outward to form the many layers of the brain. Thus, hundreds of millions of primitive nerve cells are moving to form the brain, most migrating considerable distances. Some cells travel a distance comparable to walking across the USA. The cells are guided to their specific destinations by cell genetic factors and by other specialized cells called “glia”. At the end of the process, 100 billion nerve cells will have arrived at their final destination to form the brain, each cell making as many as 1000 connections.



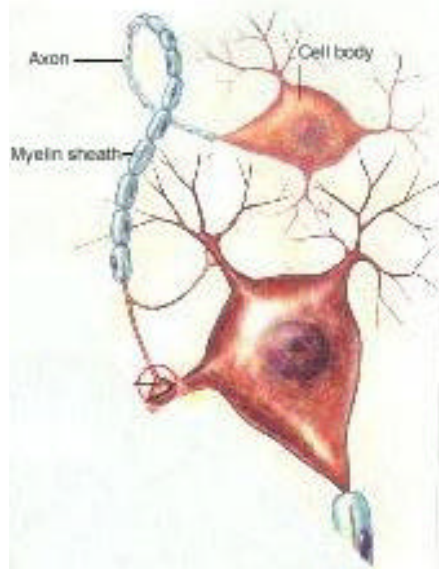
The migration road map is controlled by a number of genetic and environmental factors. If any of these factors is disturbed, serious alterations in brain structure and/or function results.

Alcohol, drugs (medicinal and recreational), products of maternal infection and inflammation, environmental toxins (e.g. lead) and radiation are all factors that can interfere with the travel of migratory cells to their proper destination. *The Foundation is in active collaboration with the government's National Institutes of Health (NIH) and its Centers for Disease Control and Prevention (CDC) to promote and support additional research in these areas.*

In addition, the Foundation is supporting a pilot research program to establish a state-wide database in which every live birth is monitored, the factors associated with developmental brain damage identified and the consequences of the brain damage evaluated in childhood, including the school environment. The research includes identifying the presence of selected genetic and environmental factors, documenting the probable time of fetal exposure, analyzing the quantitative amount of exposure, and correlating this information with the occurrence of developmental brain damage and functional disability. *The information obtained will provide the basis for identifying and testing specific hypotheses aimed at the development of interventions to prevent developmental brain damage and its consequences.*

### Poor Myelination

Brain nerve cell fibers (axons) carry messages from nerve cell bodies to the target; generally adjacent nerve cells or cells in other parts of the brain or spinal cord. The message travels at the speed of a few thousandths of a second. If the axon is poorly myelinated (insulated), the speed of message transmission is significantly delayed resulting in poor coordination of messages at the axon's end. Poor myelination can occur in the fetal brain due to hemorrhage of its very delicate blood vessels; this results in PVL: periventricular leukomalacia (peri = around; ventricular = central cavity; leuko = white matter-- the axon; malacia = poor). PVL is the result of damage to the process responsible for myelination of developing axons adjacent to the brain's central cavity; its clinical manifestations are spasticity and poor coordination of the muscles on both sides of the body (e.g. spasticity of both legs). The brain's delicate blood vessels are at the highest risk of damage in the premature infant. *What are the causes of blood vessel hemorrhage? Can they be prevented? What is the process that interferes with myelination? Can it be prevented? Can the myelination process be reactivated?*



Since premature birth is the most common situation associated with PVL, prematurity has been identified as a major target of the Foundation's program to prevent cerebral palsy.

### Prematurity

Full term birth is the result of 40 weeks of pregnancy. Prematurity has occurred if the infant is born prior to 37 weeks of pregnancy. As remarkable as is modern neonatal care for the premature infant, it continues to be a modest substitute for the maternal environment in support of the development of the fetus, particularly its brain. Although prematurity occurs in but 15% of live births, it is associated with 40% of the occurrence of cerebral palsy. Thus, prematurity is a major risk factor for cerebral palsy. Its causes are many and include maternal infection, maternal and fetal immune system disturbances, endocrine and metabolic disorders of the mother, placental pathology, and the presence of multiple fetuses (twins, triplets, etc.). *Studies are underway to understand how these factors lead to premature labor and how to intervene to prevent premature delivery.*

The Foundation's program has identified one of these factors for special attention: *low grade infection of the mother's uterus*. Low grade uterine infection often causes no signs of maternal illness and so goes undetected. Yet cellular substances (cytokines) are being produced as a result of the infection; cytokines affect uterine sensitivity and fetal brain cell development. The specific cytokines responsible (there are many cytokines) are being identified, practical methods for their identification established as an aid to diagnosis, and treatments evaluated for the underlying infection. *In addition to financial support of these studies, the Foundation in collaboration with the Little Foundation in Great Britain has assisted an international group of scientists to collaborate in this area of research and share information on a continuing basis.*

### **PERINATAL BRAIN DAMAGE**

The perinatal period includes the birthing process and the several hours immediately preceding and following it. 20% of cerebral palsy cases are associated with events that occur at this time. The process of being born is a traumatic event to the infant. A number of things can go wrong. The infant's head can be compressed while traveling through the birth canal; a traumatic passage due to a large head, a narrow canal, or poor positioning in the canal can cause an increase in intracranial pressure and result in rupture of delicate blood vessels in several areas of the brain. Circulation to the brain can be diminished due to pressure on the umbilical cord, resulting in a lack of oxygen and brain cell death. At the time of birth, failure of the infant to breath or the presence of under-inflated lungs can result in severe oxygen deprivation and brain cell death. In addition to the brain cell damage occurring during the birthing process, a yet unknown proportion of infants are born at full term with brain damage that occurred during early development and which is recognized only in the perinatal period. This is particularly true of the full term but low birth weight infant.

### Low Birth Weight

Infants born weighing less than 5.5 lbs are considered to be at low birth weight (LBW). Infants born weighing less than 3.3 lbs. are considered to be at very low birth weight (VLBW). These infants are prone to be born with developmental disorders, particularly developmental disorders

of the brain. They fall within two groups: those born prematurely as discussed above and those born at full term. Full term births account for 60% of cerebral palsy. Because 85% of live births are at full term, the risk of cerebral palsy occurring in any one infant is very small; but 4 million infants are born each year and so the cumulative effect on the number of brain injured infants is substantial. The incidence rate is small, but the number of new cases is large.

In the full term infant, being born at LBW is an important risk factor for cerebral palsy; being born at VLBW is a major risk factor for cerebral palsy. 40,000 infants are born each year at VLBW and it is estimated that 30% of VLBW infants are brain injured. *Why?* At this time, we can only hypothesize. *Is the brain injury due to the same factors that caused the VLBW? For example, are both the VLBW and the developmental brain damage due to a low level of thyroid function in the mother?* Also we know that multiple births (twins, triplets, etc.) are usually associated with LBW and VLBW. There is a four fold increase in the probability that one twin will have cerebral palsy when compared to a singleton birth; the percentages go up with increased fetal numbers. The presence of multiple fetuses is becoming an increasing problem as more women are turning to fertility enhancement procedures to become pregnant. Fertility enhancement often leads to the births of multiple LBW and VLBW infants: 3 infants, 4 infants, 7 infants. The risk of cerebral palsy in one or more of these infants is high. *Why? Is the mother's metabolism inadequate to provide for the developmental needs of more than one fetus? Can her placenta support them?* These are research areas receiving focused priority attention.

The causes and prevention of LBW and VLBW are subjects of great interest; research in these areas is being supported by a number of organizations. The Foundation's program focuses on the specific causes of cerebral palsy in these populations and the development of methods to protect the brain of LBW and VLBW infants; these methods are referred to as *neuroprotection*. As of this time, there are a number of pharmacological (e.g. steroids) and physical (e.g. brain cooling) interventions being explored to protect the threatened newborn brain. Several work, but their side effects are often unacceptable. The search continues, fostered by research consortia sponsored by this Foundation in cooperation with industry and government.

### **POSTNATAL BRAIN DAMAGE**



The brain completes its “hard wiring” in the second year of postnatal life. The brain does continue to change functionally for the remainder of life as it reacts to internal changes and external experiences, particularly at the time of puberty. These changes are brought about by alterations in the patterns of brain cell connections. However, at two years of age the brain's basic structure has been established; its physical development is at an end. During the two years of postnatal life, the developing brain can be subject to a number of insults to its motor (muscle) control system that will eventuate in cerebral palsy. The most usual of these are physical trauma (brain injury due to falls and physical abuse), infection and respiratory distress. In response to injury, old connections can be

terminated and new connections made; sometimes the ir new connections are inappropriate or not functional. The Foundation supports research in these areas aimed at the prevention of injury to the developing brain and the establishment of appropriate new connections. This support is often in cooperation with other organizations such as the National Stroke Association and the Head Injury Association.

Secondary prevention is the prevention of the impairments (e.g. muscle spasticity) and disabilities (e.g. difficulty with ambulation) resulting from developmental brain injury. It also includes the consequences of these such as pain, poor nutrition, urinary incontinence, etc. Research in secondary prevention generally addresses the development of improved methods of diagnosis, treatment and management, research areas that will be the subject of a subsequent Foundation report.

### **UCP FOUNDATION RESEARCH STRATEGY**

In order to further its prevention research program, the Foundation's strategy includes:

- seeking and acting upon the continuing advice and assistance of research leaders in the field, particularly the Foundation's Research Advisory Council.
- interacting with and sometimes being part of the research advisory structure of other organizations such as government research agencies (e.g. NIH, CDC, NIDRR), academic institutions, research institutes (e.g. Burke, Kessler, Salk, Kennedy Krieger), foundations (e.g. Hearst Foundation), industry and other organizations.
- sponsoring research workshops in which scientific leaders address a critical research question, share findings and problems, and agree to cooperate in answering the question.
- providing risk venture financial support for pilot research projects exploring new approaches to the answer of important research questions.
- funding the career development of young clinician-scientists to become the future academic leaders in cerebral palsy research, teaching and patient service.
- informing the public of the continuing advances in research for the prevention of cerebral palsy and improving the quality of life of persons with disabilities due to developmental brain damage.

**UCP-REF; 2002**

**Note: The Drawings on page 2, 3, and 5 are reproduced from "The Secret Life of the Brain" with the permission of its author, Richard Restak, M.D. The Dana Press and Joseph Henry Press (2001)**