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THE COLLABORATIVE PERINATAL PROJECT: A 50-YEAR RETROSPECTIVE

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Fifty years after recruiting its first pregnant woman, the Collaborative Perinatal Project (CPP) remains a landmark in American maternal and child health epidemiological research. No U.S.-based study of pregnancy and childhood conducted before or since has matched its size, breadth and depth. The shadow of the CPP even looms long over the soon-to-begin-enrollment National Children's Study (NCS). The very concept of the NCS began at a small Federal planning meeting in 1998 when someone said “It's been 40 years since anyone has tried to conduct a large pregnancy cohort study in the United States,” and it is almost certain that the NCS and CPP will continue to be compared. When appropriate, I will draw parallels between the trials and tribulations of the CPP and those of the NCS.

History of the CPP

A reflection on the history of the CPP from the perspective of one who was actually there was written in 2003 by Janet Hardy, Principal Investigator of the Johns Hopkins CPP site.[1] I was *in utero* when the first CPP funds were appropriated and was preparing to enter kindergarten when the first woman was enrolled. My history must of necessity come second-hand, from anecdotes told to me by Heinz Berendes, my mentor at NICHD who in his former position as Chief of the Perinatal Research Branch at the National Institute of Neurological Disorders and Stroke (NINDS) directed the CPP.

The post-Second World War years saw the confluence of several factors. It was a time of relative peace and prosperity in the United States, during which the government began to expand its activities in a variety of domestic areas including medical research. Expansion of research combined with the invention of the mainframe computer to foster the development of the modern prospective cohort study, as exemplified by the Framingham Study.[2] This era was characterised by recognition that while improvements in sanitation, public health and medical care had brought about large declines in maternal and post-neonatal (28−364 day) mortality over the first half of the 20th century (from 1901 to 1950), fetal/infant mortality from 20 weeks' gestation to 27 postnatal days had declined much less.[3] The 1950s was also a time of relatively stagnant infant mortality.[4]

In a series of articles, Abraham Lilienfeld and his co-investigators[5,6] argued that there was a “continuum of reproductive casualty” that started with miscarriage, continued through stillbirth, neonatal death, non-lethal birth defects, preterm delivery, cerebral palsy and mental

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retardation, and ended with milder conditions such as learning disabilities. Lilienfeld[5] described the 2 prevailing views of developmental disability. One, originally proposed by the orthopaedic surgeon William Little, held that events associated with birth such as injury, asphyxia and preterm birth were the major cause of cerebral palsy and severe mental retardation. The other, proposed by Sigmund Freud before he became famous as a psychiatrist, held that these conditions were of developmental origin and the same conditions that caused abnormal birth also caused neuro-developmental disability. It is interesting to think that these conflicting views are still with us today as we in perinatal epidemiology struggle to integrate the concept of "fetuses at risk" into our thinking.[7]

The National Institute of Neurological Diseases and Blindness (NINDB, now the NINDS) was founded in 1950. The first NINDB director, Pearce Bailey, recognized that the time was right for a major research effort by a multi-disciplinary team to determine how medical, environmental ("family situation, socioeconomic factors"[8]) and genetic factors combined to cause of the continuum of reproductive casualty. In 1953, Congress appropriated funds to begin the planning of a large, multidisciplinary study with the name "The Collaborative Investigation on the Clinico-Pathologic Correlation in Cerebral Palsy, Mental Retardation, and other Neurological Disorders having their Origin in the Perinatal Period." As the Study's multidisciplinary nature and the broad context within which neurodevelopment is expressed became clear, the name was changed to "The Collaborative Study on Cerebral Palsy, Mental Retardation and Other Neurological and Sensory Disorders of Infancy and Childhood."[3] It has since been unofficially shortened to "The Collaborative Perinatal Study," or "The Collaborative Perinatal Project." (The word "national" has never appeared in any official name.) As Dr. Hardy notes, the CPP was always included as a "line item" in the NIH budget, which can be both a blessing (by protecting it from any Agency-level hostility that might have existed) and a curse (by rendering it susceptible to the Congressional budgeting process).[1]

During planning, input was solicited from the scientific community, members of Congress and members of "informed lay groups" such as the United Cerebral Palsy Association, Inc. In 1956, Dr. Bailey established the first of many *ad hoc* committees to develop and review the study protocols. Planning continued for several contentious years[1] and in January 1958 the first pilot woman was enrolled. Procedures continued to be fine-tuned. For example, the original question on time-to-pregnancy was "How long did it take you to get pregnant?" When a woman answered "30 seconds," the question was re-phrased. (Heinz Berendes, personal communication). The first study woman was enrolled on January 2, 1959. The multi-disciplinary nature of the CPP led to inevitable difficulties getting investigators from diverse fields to speak the same technical language and even to respect each other.[1] This presaged similar difficulties experienced by the NCS.[9] As one of the individuals charged with developing the NCS, it was perversely comforting to know that interdisciplinary frustrations were nothing new! Similarly, the extended gestation, wide solicitation of input and reliance on numerous external advisory committees marks another parallel between the CPP and NCS.

Over the years I have searched the extensive CPP documentation for specific null and alternate hypotheses, and could find none. Nevertheless it would be unfair and inaccurate to state that the CPP lacked focus. The CPP synopsis[8] states

> The causes of certain disorders and conditions affecting children—cerebral palsy, epilepsy, mental retardation, defects of speech, hearing, and vision, organic behavioral syndromes, reading and learning deficiencies—are for the most part unknown. There is strong belief that the origins of these conditions lie in factors that come into prominence or in events that occur during the time period between conception and the early months of life and moreover, that these factors or events are the precursors of congenital malformations and prematurity, (*sic*) or in the extreme case, fetal and neonatal death.

The synopsis goes on to state

> Perinatal factors and conditions to be investigated include: 1) the conditions of the pregnancy itself, such as infection, trauma, drug reactions or the progress of labor. These include normal and abnormal physiology of pregnancy, labor and delivery; 2) the environmental factors- social and economic conditions, emotional stress, or medical care- influencing parents; 3) the biological factors – age, medical and reproductive history, immunologic characteristics – in parents; 4) the genetic background of the parents.

So while the CPP may not have had a specific "rifle-shot" hypothesis, it most definitely had a coherent set of aims and risk factors to be investigated. Indeed, many of the investigations posited above remain active areas of research in the maternal and child health epidemiology community. I do not believe the lack of a specific hypothesis to be a major flaw—it's hard for me to imagine any single hypothesis that by itself would justify the massive expenditure of time, effort and funding that the CPP (or any other large, complex cohort study) required.

Big Science often attracts Big Enemies, and as was the case with the Women's Health Initiative[10] and the Supercollider,[11] the CPP had its share. As detailed by Dr. Hardy, numerous well-respected academics argued strongly that the considerable monies spent on the CPP would be invested more wisely in many small, investigator-initiated projects.[1] Even before it has begun enrollment, the NCS has attracted similar criticism.[12] Concerns were also raised that the broad goals of the CPP amounted to a poorly directed fishing expedition and that the quality of the data was poor.[13] The persistent drumbeat of criticism resulted in three external scientific committees being established over the years to review the CPP, and the entire study was nearly terminated just as the final follow-up was being completed .[1] Partly as a result of the extensive scrutiny, validation studies of the quality of the CPP data were undertaken, and in fact the data were determined to be of high quality.[3]

Unfortunately, old rumours die hard, and over the years many professors of paediatrics and obstetrics (almost all of whom are now professors emeriti) have told me in so many words that the CPP "had no hypothesis," "was a boondoggle," or "was garbage in and garbage out." Even a long-serving senior NIH official recently (and privately) reflected on the CPP as "a disaster." Fortunately, I've never heard such complaints from professors of epidemiology, who have better understanding of what can be done in a large prospective cohort that cannot be done in the hospital ward or at the laboratory bench. Nevertheless, the common (and untrue) belief that the CPP represented undirected data collection may have been responsible for the NCS' decision to adopt explicit and highly-reviewed Core Hypotheses.[14]

Structure of the CPP

Just as I have never found a specific study hypothesis, I have never found evidence that a formal sample size calculation was done. Dr. Berendes did, however, tell me that recruitment was based on the desire to assemble 200 children with cerebral palsy, which set a goal of 40,000 surviving children successfully followed, requiring recruitment of approximately 50,000 pregnant women. The issue of statistical representativeness was a thorn in the side of the CPP almost from the beginning. The study synopsis from 1966 states:

> The design of the Collaborative Project did not call for the development of incidence or prevalence rates of events during pregnancy or delivery or the insurance of the adequacy or representativeness of the sample of Study patients from the general population of the community or of the Study hospital.
>
> It did, however, require the selection of cases in such a manner as to cover the broad spectrum of pregnancy conditions represented by the Study populations. It was to be

> designed to produce a selection free from the induction of special cases based on individual institutional interests. To use selection procedures that would interfere as little as possible with the routine of the maternity clinic or office and promote continuing follow-up of the children has been imperative....

Each of the 12 recruiting institutions had its own defined sampling frame, which started with all clinic or practice obstetrical registrants and usually excluded *a priori* women whose children for various reasons were believed to be especially difficult to follow-up, such as women planning to place their child for adoption. While the sampling frames may have been driven by convenience, study recruitment itself was not. Extensive procedures and audits were established to assure that recruitment was representative of the sampling frame. The NIH made a conscious decision to conduct the CPP in academic centres, which made it more convenient to involve subject matter experts and maintain follow-up at the expense of community base and statistical representativeness.[15] This decision has long been cited as one of the shortcomings of the CPP,[16] although I am not aware of any CPP result that the "convenience cohort" design caused not to apply to the general US population of pregnant women and children of that era. This is yet another case where the CPP cast a long shadow, as the identical issue arose regarding the design of the NCS. Amazingly, both those for and against representative sampling cited the CPP in support of their arguments.[17] After much debate, it was decided that the NCS will be a statistically representative sample of U.S. births; time will tell whether the additional investment required to achieve representativeness was worthwhile.

One aspect of the design of the CPP stands in marked contrast to that of the British Perinatal Mortality Surveys of 1946 and 1958. The CPP recruited women from 12 clinical sites as early in pregnancy as feasible in that era—usually at their initial antenatal visit. In contrast, the British Surveys recruited at the time of delivery all women giving birth in a specified week. The CPP investigators realized that routine obstetrical records varied substantially from clinic to clinic and often were woefully incomplete for research purposes. They also recognised that the optimal research design demanded that data be collected as soon as possible after the event being recorded, and particularly that data on exposures should be collected before the outcome was known. Finally, they were interested in conducting serological studies to determine the role of congenital viral infection in childhood neurodevelopment, which required collecting maternal serum at least early in pregnancy and again at delivery. Therefore the need to recruit the cohort during pregnancy was never in doubt as far as I know. Again, this reflects the decision to favour prospective data collection by specifically trained individuals over national representativeness. While identifying a sampling frame for live births is straightforward, identifying such a sampling frame for pregnant women is not, especially in the de-centralised U.S. health care system. This problem provoked much discussion during the design of the NCS as well.[18]

In looking back over the CPP, one has to be impressed by the degree to which resources allowed a "brute force" approach to data collection. The Project took the remarkable step of supporting independent observers (usually registered nurses or moonlighting medical students), armed with data forms and stopwatches, who had no responsibilities other than to follow standardised procedures to document all events occurring in the labour and delivery rooms and obtain precisely timed Apgar scores. Children's parents or guardians were interviewed on numerous occasions during the course of the study. Every time the parent/guardian reported that the child had a physician or clinic visit, no matter how trivial the illness, the Project Director at that site wrote a personal letter to the treating physician or clinic requesting a copy, or at least a summary, of the medical records from the visit. The same procedure was followed when the pregnant woman reported a non-study physician or clinic visit. Amazingly, the treating physician virtually always responded and as far as I can tell, never charged a fee for the records

or the summary! In our modern era, it is simply inconceivable to me that, even if privacy and HIPAA concerns could be addressed, physicians would be this cooperative.

Families who moved away were offered the opportunity to continue their participation at another study site, if feasible. In an era when air travel was an exotic luxury, the CPP allocated funds to purchase airline tickets so that children and their parents who had moved out of range of all study sites could be flown back to their original site for psychological testing (Heinz Berendes, personal communication). The fraction of surviving children successfully followed was 88% at one year, 75% at four years and 79% at seven years.[15] Neurological examinations were done at home visits for 50 consecutive children who missed their scheduled one year visit, which enabled the Project to report that children who missed the visit were by and large normal.[19]

Another example of "brute force" data collection that in my opinion contributed (albeit perhaps inadvertently) to the enduring value of the CPP was its extensive use of free-text data. Although the CPP relied on structured, closed-ended data forms that could be entered on literally millions of 80-column punch cards before being transferred to tape, physicians, nurses and lay interviewers were all encouraged to follow-up any positive response with a text narrative. Although never computerised, these extensive free text entries enabled investigators to review the study microfilms to glean critical details about diagnoses and conditions. The enormous amount of non-computerised detail almost certainly is what enabled the CPP to play such a critical role in defining the epidemiology of cerebral palsy[20] and of birth defects;[21] the CPP is probably the best epidemiological data set for the study of congenital heart disease in the pre-echocardiography era.[22]

Important findings of the CPP

The NINDS maintained a catalogue of CPP publications until 1985, listing 569 entries (attached to this article as an on-line supplement), and Matthew Longnecker of the National Institute of Environmental Health Sciences, NIH has updated the CPP bibliography until 2006.[23] The CPP findings that have influenced current thinking in perinatal epidemiology and obstetric and paediatric practice are probably too numerous to detail, and of course the importance of any finding can be determined only with many years of hindsight. I believe that the most important findings of the CPP are

- Events of labour and delivery are not major contributors to the occurrence of cerebral palsy nor most other neurodevelopmental disorders in children. Rather, most of these conditions have their origins before labour began.[20] This finding was almost certainly opposite to what the study initiators expected to find, but has been confirmed in other studies.[25]
- Although frightening to witness, simple febrile convulsions are a common (occurring to around 3% of children) and benign event of childhood.[25] CPP publications on this topic caused an immediate and dramatic change in how paediatricians approached this condition.[26] In fact, Jonas Ellenberg told me that he once did an informal calculation and estimated that the money saved by eliminating neurologist consultations, electroencephalograms and prophylactic phenobarbital for children with febrile convulsions more than paid the cost of the entire CPP (personal communication).
- Intrauterine inflammation is a major cause of adverse pregnancy outcome.[27] This finding was met with scepticism because organisms were not often isolated from the membranes and those that were isolated were thought to be mere vaginal contaminants.[28] It was not until years later, with the advent of modern microbiological techniques, that the association came to be accepted.[29,30]

- Neonatal jaundice, even in the absence of clinical signs of bilirubin toxicity, is associated with long-term neuro-developmental sequelae. This conclusion from CPP analyses conducted in the 1960s and 1970s[31,32] formed the basis for aggressive treatment of jaundice in normal term newborns that was the rule during the 1970s and 1980s
- Neonatal jaundice in the absence of clinical signs of bilirubin toxicity is not associated with major long-term neuro-developmental sequelae. This conclusion, based on early 1990s re-analyses of the original CPP data,[33] formed the basis for the “kinder, gentler” treatment of jaundice in normal term newborns that is practiced today. Neither of these analyses could have been done had the CPP not obtained bilirubin values in every newborn according to a specific protocol.
- Sudden infant death syndrome was not a random event, and its occurrence was elevated when the mother smoked. Some of the earliest epidemiological studies of SIDS in the United States were conducted within the CPP,[34,35] and one could argue that most epidemiological research on SIDS conducted between 1976 and the discovery that prone sleeping was a cause of SIDS served merely to confirm results originally found in the CPP.
- Eastman and Jackson's report[36] that the then-common practice of restricting pregnancy weight gain was associated with an increased risk of low birthweight caused an immediate re-evaluation of this practice. CPP data also indicated that the optimal weight gain during pregnancy varied according to pre-pregnancy weight.[37] CPP results were cited by the Institute of Medicine in drafting its 1990 recommendations on pregnancy weight gain.[38]

Oversights—what might have been

Every study has oversights, things not included either because the investigators simply forgot them or made a well-reasoned decision that in retrospect was incorrect. The CPP's largest oversight undoubtedly was its failure to collect data on maternal alcohol consumption during pregnancy, beyond a single variable for whether she was a clinically-recognised alcoholic (which almost certainly was under-ascertained). It would have been very easy to add a few questions, similar to those already asked about smoking, about drinking to the interview conducted at each antenatal visit. If participant burden had been a concern, the alcohol questions could have replaced such under-analysed gems as “air travel” or “sick pet at home” that were asked at these visits. The CPP thus missed the opportunity to become the benchmark for study of the long-term subtle developmental effects of fetal exposure to ethanol. At one point I asked Dr. Berendes whether this was a simple oversight and he told me that in fact the investigators gave the issue extensive consideration before deciding that 1) women probably would not report honestly and 2) they should follow the advice of several of their advisory boards, all of whom assured them that alcohol consumption during pregnancy was not important!

The Future

Do the extant CPP data have a future? The catalogue of CPP publications[23] shows 77 from 1990−1999, an average of 7.7 per year. There were 83 publications from 2000 to 2006, an average of 11.9 per year. As more investigators acquire copies of the public-domain dataset and documentation, the number of papers seems likely to hold steady or increase. I am confident that we have not yet learned all that the CPP has to teach us. Nevertheless, investigators must be mindful of its age, and choose their topics carefully. For example, it is likely that the causes of pregnancy complications such as spontaneous preterm birth and pre-eclampsia have not changed in 50 years, although the management of the preterm infant or woman with pre-eclampsia has changed dramatically. Anyone planning a CPP-based investigation must

consider the degree to which changes in practice render their results obsolete. I believe that for most aetiological research the age of the CPP is largely irrelevant; the less-aggressive treatment of many pregnancy complications and relative infrequency of labour induction or caesarean section make the CPP particularly relevant for studying the aetiology of conditions for which medical management distorts the natural history. With these caveats, there is a lot of life left in the CPP.

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