INTRODUCTION

Most countries use a large fraction of their financial commitment to disease prevention on activities related to the reproductive period. Much less is spent on the research needed to make this prevention evidence-based. Most of the research on reproductive health in the past has focused on cause-effect relationships which span from conception to the first months of life—primarily determinants of fetal growth, reduced pregnancy duration, spontaneous abortion, and congenital malformations. Recently, research activities have also focused on proximal determinants of the biologic ability to reproduce and on long term consequences of the intrauterine hormonal environment or intrauterine growth retardation. In order to address many of these research problems, we need studies with long term follow-up, starting as close to conception as possible.

There are now good reasons to believe that the etiologic factors for many chronic diseases accumulate over a person’s entire lifetime, and that factors related to embryonal and fetal life are important, perhaps even of crucial importance (1). For most chronic diseases, we are only able to account for a small fraction of incidence and prevalence using the knowledge we have on established risk factors, perhaps because we have not taken the fetal period of life into consideration.

HEALTH OUTCOMES

Fecundity

Humans now have a vast overcapacity to reproduce in comparison with what is needed to maintain the species’ population size under the present conditions, and overpopulation is a serious public health problem in many parts of the world. For this reason, etiologic research on fecundity did not receive much attention until the 1970s and 1980s (2, 3). Time-to-pregnancy studies were only introduced into epidemiology in the early 1980s (3, 9), although demographers had used time from marriage to the birth of the first child as a fecundity measure in the past.

The identification of 1,2-dibromo-3-chloropropane as a cause of reduced sperm concentrations (10), and later a meta-analysis of studies of declining sperm counts whose results had been published during the past 60 years (11), moved the debate forward in the public media. 1,2-Dibromo-3-chloropropane is now a well accepted cause of impairment of sperm production, but a decline in sperm counts was also soon taken as fact, which it is not (12). However, because the absence of evidence is not evidence of absence, the decline could be real; and if this is so, much more research is needed, since average sperm counts are close to a level at which even a small reduction may impair fecundity (13).

The known determinants of low sperm counts are few, and they do not explain the differences we see between populations, nor do they explain a possible
decline in sperm counts over time. However, it has been suggested that the level of prenatal estrogen exposure (or perhaps the balance between estrogen and progesterone levels) is the main determinant of the number of Sertoli cells present at birth, and thus a determinant of sperm concentrations in adult life (14). External sources of hormonal disrupters and other sources of exposure may have increased over time, and if these are present during pregnancy, this may explain a possible reduction in sperm counts.

Whether human fecundity is declining is still an unsettled issue, but work in this field has identified a number of risk factors that operate over shorter time periods—for example, sexually transmitted infections, smoking, alcohol intake, high body mass index, heavy exercise, and a number of environmental and occupational exposures (3, 9, 15). Researchers have started to scrutinize the estrogen hypothesis and the importance of other prenatal factors related to reduced fetal growth. One study indicated that prenatal exposure to maternal tobacco smoke impairs female fecundity (16). This finding needs to be confirmed.

The next few years will show us whether taking a life course approach in this research, by including potential prenatal determinants, will provide more insight. Studies of male offspring born to women who used the potent estrogen diethylstilbestrol during pregnancy have not shown low sperm concentrations (17), which would be expected according to the estrogen hypothesis. However, it will be interesting to study sperm concentrations as a function of markers of fetal exposure to estrogen—for example, birth weight, twinning, parity, or maternal age or diseases such as hypertension, preeclampsia, and hyperemesis.

At the same time, it will be important to set up a monitoring system that follows developments in fecundity over time, which is not an easy task. The best solution is probably to conduct regular fertility surveys based on highly structured questions on fecundity, and to obtain representative samples of semen, which may be possible in some parts of the world. Countries that run regular censuses could add questions on unsuccessful pregnancy attempts and time to pregnancy. It should be fairly simple to develop standardized questionnaires if we use current experience (18).

Cancer

It has been suggested that a high level of endogenous or exogenous estrogen exposure during gestation may be a cause not only of low sperm counts but also of cancer of the testis and of hypospadias (14). The incidence of cancer of the testis in Denmark is 9.3 per 100,000 man-years. Most cases are diagnosed in men aged 20–49 years, but carcinoma in situ has been seen even in early childhood (19). Cancer of the testis is more frequent among firstborns, and the incidence increases with maternal age (20). If low sperm counts and cancer of the testis have a common prenatal etiology (21), it may operate through higher endogenous estrogen levels in fetal life. A higher incidence of testis cancer in infertile males supports the estrogen hypothesis to some extent; other cancers (breast and prostate cancer) have shown a tendency towards a higher risk associated with high birth weight and jaundice (22). A decreased risk of breast cancer has been seen for conditions associated with low estrogen levels, such as preeclampsia and prematurity (23).

Childhood cancers are rare and therefore difficult to study, but the most consistent risk indicator has been an association between high birth weight and childhood leukemia (24). The current hypothesis is that growth factors increase the number of stem cells and thus the number of cells at risk of malignant transformation. Breast cancer is more frequent in Caucasians than in Asians, perhaps because of differences in the size of their mammary glands, since breast reduction surgery has been shown to reduce risk (25). Higher birth weights and placental weights have been associated with increased breast parenchyma (26). It is also possible that increased cell division driven by growth hormones increases the risk of first-stage malignant transformations of cells through changes in different hormonal receptors.

It has only been 10 years since Trichopoulos suggested that breast cancer originates in utero (27). Since then, several studies have attempted to correlate cancer incidence with proxy measures of perinatal events or growth parameters. Recently, Adami et al. (28) proposed an etiologic model with four elements: 1) cancer risk depends on the number of cells at risk; 2) responsiveness of target cells to hormonal stimulation is partially determined early in life, perhaps in utero; 3) pregnancy stimulates the replication of initiated cells but provides protection through cellular differentiation; and 4) mammatropic hormones preserve spontaneous somatic mutations and stimulate initiated clones.

Fetal growth and cardiovascular disease

The most attention has been given to the possibility of a fetal (or early) origin of cardiovascular disease, mainly because of the findings of Forsdahl (29) and Barker (30). The basic concept of such “programming” is simple and convincing: The fetus adapts to undernutrition by redistributing the blood flow to secure the development of the brain and develops insulin resistance to reduce growth. Newborns will be thin, with a disproportionately low birth weight, unless
fetal adaptation takes place early in pregnancy. If the necessary energy supply is cut off or is insufficient at critical stages of organ development, this could permanently alter organ development by changing the cell distribution, which may alter functioning and thus increase disease susceptibility later in life. In principle, this mechanism may play a role in many diseases. The first circumstantial evidence for a programming effect came from macroepidemiologic studies in Norway in which Forsdahl (31) showed that middle-aged males had higher cardiovascular disease mortality if they had been born in regions where the infant mortality at that time was high. Forsdahl suggested that social factors were responsible for the association; this explanation is a possible alternative to the programming theory. It was also intriguing when another study found a similar correlation between birth in a region with high infant mortality and serum cholesterol levels (31).

Animal studies have focused directly on fetal nutrition and subsequent organ functioning. These studies have shown that the administration of a low protein diet to pregnant rats affects the size and DNA content of different organ systems (32, 33).

A lack of energy supply during fetal life may have many causes, such as an inadequate intake of nutrition by the mother, disease during pregnancy (e.g., hyperemesis or malabsorption), or an exposure such as smoking. Most of the epidemiologic studies on fetal origins of human diseases are based on microepidemiologic studies linking historical data from routine birth registration to measures of organ functioning or overt diseases. In general, these studies show that low birth weight or indirect markers of disproportional growth are associated with cardiovascular diseases or the presence of a high cardiovascular disease risk profile, such as glucose intolerance, insulin resistance, and diabetes mellitus (33). However, not all studies corroborate these findings (1). The fact that birth weight apparently correlates with a large number of adult health conditions is also of some concern, since it violates the principle of specificity in a cause-effect relationship (34).

Most of these studies have a number of shortcomings. None of the data sets have been designed for studying fetal programming, and in general the exposure measures are far from optimal. Follow-up has been poor in many studies, and the possibilities for controlling confounding by postnatal risk factors have been inadequate. On the other hand, we have now results obtained from several studies in different countries (1). However, the theory fails to explain all observations.

It is not at all clear how the programming hypothesis helps to explain the rise and fall of rates of cardiovascular disease seen in many countries or the large differences in morbidity and mortality observed between different countries. On the other hand, a low incidence of cardiovascular disease in, for instance, developing countries may be explained by proportionally reduced fetal growth, with an adaption to the energy supply seen in some of those countries. Alternatively, the reason could be an absence of proximal determinants of cardiovascular diseases like obesity, a diet rich in saturated fat, etc. For example, cardiovascular disease among Inuits seems to increase following the adoption of a more “Western” diet and lifestyle (35). However, the main problem is that the existence of several sex-specific growth measures at different ages provides analytical options and a high probability that one of these options will be associated with the disease regardless of causality. Without specific prior hypotheses, the findings do not have high credibility.

Furthermore, most of the studies have had no information on determinants of fetal and childhood growth. Therefore, the next research step is to establish cohort studies that include not only dietary factors during pregnancy but also other factors of importance for fetal growth. The National Birth Cohort in Denmark has this aim. Studies of pregnant women with diseases that may interfere with fetal nutrition are also of interest, such as studies of children born to mothers after hyperemesis gravidarum or to mothers who suffer from diseases leading to chronic malabsorption (36).

Cognitive function

If the function of the liver or the pancreas is programmed during fetal life, then the same may be true for the brain, although we expect the brain to be better protected than other organs. Shortage of food leads to an unequal distribution of energy, which favors the brain. We know that severe lack of energy to the brain may result in permanent damage (37), but whether a more moderate impairment of energy supply causes loss of brain functioning is an open question. Research has shown that cognitive function is almost linearly associated with birth weight up to 4,000 g (38), but these analyses may easily suffer from uncontrolled confounding by social factors.

It is perhaps more promising to look for specific exposures, whether or not these exposures are of a dietary nature. We know that high levels of alcohol intake during pregnancy are associated with mental retardation, and we expect alcohol or its metabolites to be the neurotoxic culprit (39), but we cannot rule out the possibility that lack of specific dietary factors may also play a role. Alcohol replaces other sources of energy, and alcohol abuse is often accompanied by very poor dietary habits.

Several studies have shown that breast-fed children score higher on cognitive tests than formula-fed chil-
dren (40, 41), and several mechanisms may be involved. The psychological hypothesis favors the close mother-and-child contact of breastfeeding. The genetic hypothesis states that women who breastfeed have higher intelligence quotients and that breastfeeding mothers may pay more attention to the child and to the need for cognitive training. However, randomized trials have shown that dietary factors may be important. Preterm boys fed on enriched formula had better cognitive function 8 years later than boys fed on standard formula (42, 43). A spurt in brain growth takes place in late pregnancy and the first years of life, and trials indicate that specific micronutrition such as n-3 fatty acids (44) may play a role during the last trimester of pregnancy. Most studies on the importance of dietary factors during pregnancy have not been large enough or focused enough. It is past time to begin such studies.

DISCUSSION

It is well known that cumulative exposure over time is often needed to cause the onset of a disease. Diseases that have no single necessary or sufficient cause in the strict sense must have several causes (45). In fact, the presence of four component causes is the minimum requirement for producing associations which “only” have a probabilistic nature. Some of these component causes may start to operate during gestation. The pathogenic process may need to reach a certain level to produce clinical symptoms, as in atherosclerosis; or a number of cellular transformations may be needed to start a disease process, as in cancer, and these transformations may require a specific set of exposures. We know something about the proximal determinants of many chronic diseases, but in general we cannot explain more than a fraction of the disease variation in different subdomains of the population. We expect these proximal determinants to act on a set of conditions, which we call susceptibility. This susceptibility may be shaped by our genetic constitution or by other exposures that programmed organ functioning early in life.

It is not unexpected that the period of organogenesis or the period of rapid cell growth is more important than other periods. In spite of radical improvements in maternal and infant mortality, the perinatal window is still a high risk time period, and most countries expend large amounts of resources on antenatal care. Most of these activities have been directed towards the prevention and early treatment of diseases which manifest during pregnancy or shortly thereafter. We know from animal experiments that prenatal exposure often has delayed effects in offspring. We should also expect this to be the case in humans, more often than is known at present. Long term follow-up of newborns should be undertaken to examine this possibility.

It is not unreasonable to expect the cellular structure of organs to depend partly on the intrauterine environment and not only on the genes coding the building blocks. Exposure to teratogens may similarly cause not only a condition such as malformation but also an impairment of organ functioning. Any change in function may be a sufficient cause for a later onset of a disease, or it may form part of a causal field that in combination causes the disease. The latter situation requires additional component causes, and studying disease etiology requires a long follow-up period, perhaps a lifelong perspective. Organ programming may in this case be a weak determinant of, for example, diabetes if the adult determinants such as lack of exercise or a high fat diet are not present. Neurotoxic exposures that only affect subtle brain functioning will only be manifest when this functioning is needed, and might never be detected if cognitive or behavioral functioning is within normal limits.

CONCLUSION

Cumulative exposure over the life span probably plays a role in many chronic diseases. Recent research indicates (30) that the embryonal and fetal period is of particular importance. In view of this, we need to reconstruct the infrastructure for epidemiologic research. The time has come to set up once more large cohort studies with follow-up beginning as close to conception as possible. The cohort studies should allow long term follow-up but also permit studies on diseases like congenital malformations, asthma and allergies, and mental and behavioral disorders in childhood. These studies should include assessment of DNA and other biologic material which will permit measures of environmental exposure. The mapping of the human genome and the new options of using blood spots on filter paper and making multiple measures on small amounts of biologic material carry great promise for the cost-effectiveness of such studies.

The incidence of cancers of the breast and testis is rising in many countries, and we do not know why. It is possible, perhaps even likely, that we should seek explanations for causation early in life. New environmental exposures accumulate through the food chain, and new drugs are being introduced all the time. All of these influences could have short term or long term side effects during pregnancy that should be studied.

Not only do we need to collect longitudinal data over long time spans but we also need to organize access to research data in a way that permits several generations of epidemiologists to work with the database. We will probably have to negotiate different
rules for funding, data protection, and obtaining informed consent. Since consent must be informed, some ethics committees have required that the information provided to participants be specific. They have not accepted more general statements addressing an overall purpose or considered the possibility that the participants themselves should decide whether they will accept a general statement for the aim of the study. A long term follow-up study should be used to address many specific objectives, and most of these objectives will not be known at the start of follow-up. In general, much important research was not foreseen when investigators were setting up many of the well known long term follow-up studies, such as the Framingham Heart Study or the Nurses’ Health Study. Although the consent provided for such studies cannot be specific, it need not be without direction. It is reasonable to specify on the consent form that the data collected can only be used with a general public health aim. Use of such data for commercial purposes is not acceptable.

This avenue for research raises new opportunities for prevention, but the fruits of this investment will not be seen until well into the new millennium. Planning must start now so that we do not waste valuable time. If we wish to promote evidence-based prevention, we must start now so that we do not waste valuable time. In general, much important research was not foreseen when investigators were setting up many of the well known long term follow-up studies, such as the Framingham Heart Study or the Nurses’ Health Study. Although the consent provided for such studies cannot be specific, it need not be without direction. It is reasonable to specify on the consent form that the data collected can only be used with a general public health aim. Use of such data for commercial purposes is not acceptable.

This avenue for research raises new opportunities for prevention, but the fruits of this investment will not be seen until well into the new millennium. Planning must start now so that we do not waste valuable time. If we wish to promote evidence-based prevention, we must start now so that we do not waste valuable time. In general, much important research was not foreseen when investigators were setting up many of the well known long term follow-up studies, such as the Framingham Heart Study or the Nurses’ Health Study. Although the consent provided for such studies cannot be specific, it need not be without direction. It is reasonable to specify on the consent form that the data collected can only be used with a general public health aim. Use of such data for commercial purposes is not acceptable.

This avenue for research raises new opportunities for prevention, but the fruits of this investment will not be seen until well into the new millennium. Planning must start now so that we do not waste valuable time. If we wish to promote evidence-based prevention, we must start now so that we do not waste valuable time. In general, much important research was not foreseen when investigators were setting up many of the well known long term follow-up studies, such as the Framingham Heart Study or the Nurses’ Health Study. Although the consent provided for such studies cannot be specific, it need not be without direction. It is reasonable to specify on the consent form that the data collected can only be used with a general public health aim. Use of such data for commercial purposes is not acceptable.

This avenue for research raises new opportunities for prevention, but the fruits of this investment will not be seen until well into the new millennium. Planning must start now so that we do not waste valuable time. If we wish to promote evidence-based prevention, we must start now so that we do not waste valuable time. In general, much important research was not foreseen when investigators were setting up many of the well known long term follow-up studies, such as the Framingham Heart Study or the Nurses’ Health Study. Although the consent provided for such studies cannot be specific, it need not be without direction. It is reasonable to specify on the consent form that the data collected can only be used with a general public health aim. Use of such data for commercial purposes is not acceptable.

ACKNOWLEDGMENTS

The activities of the Danish Epidemiology Science Center are financed by a grant from the Danish National Research Foundation. This work was additionally supported by grant JN 12-1663-1 from the Danish Medical Research Council.

REFERENCES