CONFERENCE ON

Maternal & Newborn Nutrition & Health

RADISSON SOUTH
BLOOMINGTON, MN

May 6-7, 1976

ACKNOWLEDGEMENT

We acknowledge with deep appreciation the financial contribution of the National Foundation-March of Dimes Metropolitan Minnesota Chapter, the Maternal and Child Health Program of the School of Public Health-University of Minnesota, Ross Laboratories, and Mead Johnson to the 1976 Conference on Maternal and Newborn Nutrition and Health, and the time and effort put into planning the Conference by the Maternal and Infant Committee of the Minnesota State Nutrition Council and the Nutrition Committee of the Academy of Pediatrics.

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CONFERENCE ON MATERNAL AND NEWBORN NUTRITION AND HEALTH

CONFERENCE PURPOSE:

Develop an awareness of the magnitude of health problems encountered during adolescent pregnancies.

Develop an interdisciplinary approach dealing with needs of the pregnant adolescent

Identify nutritional needs and recommended dietary practices for the adolescent

Identify neonatal and infant needs and services for infants at risk

ACCREDITATION: The program is accepted for 5 hours Continuing Education credit to registered dietitians. The Continuing Medical Education offering meets the criteria for 6 hours of credit in Category I for the Physicians Recognition Award of the AMA. Approval has been requested for 6 elective hours by the American Academy of Family Physicians.

THURSDAY, MAY 6

p.m.

5:30 Conference registration begins
6:00 Social hour—courtesy of Ross Lab
7:00 Dinner (Arnold Anderson, presiding)
Speaker—Myron Winick
"Infant Nutrition & Subsequent Development"

FRIDAY, MAY 7

a.m. (Betty Ruth Carruth, presiding)

8:00 Registration
8:30 Pedro Rosso
"Nutrition Related to Fetal & Neonatal Growth"
9:25 Janet C. King—"Nutrient Needs During Pregnancy"
10:20 Nutrition break—courtesy Mead Johnson Laboratories
10:45 Myron Winick—"Nutrition & Mental Development"
11:40 Additional Questions for Winick, King, and Rosso
12:00 LUNCH

p.m. (Katherine Goodman, presiding)

1:15 Roy Pitkin—"Intra-uterine Growth Retardation"
2:15 Nutrition break—courtesy Mead Johnson Laboratories
2:45 Panel: "Interdisciplinary Approach to Adolescent Pregnancies"
Muriel Caldwell—Nutritional
Michael Baizerman—Sociological
John Reynolds—Neonatal
Emanuel Gaziano—Maternal

THE FINANCIAL ASSISTANCE OF THE NATIONAL FOUNDATION OF THE MARCH OF DIMES AND THE UNIVERSITY OF MINNESOTA SCHOOL OF PUBLIC HEALTH IS GRATEFULLY APPRECIATED.

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INFANT NUTRITION AND SUBSEQUENT DEVELOPMENT

Myron Winick, M.D.*

INTRODUCTION

Two developments over the past few years have highlighted the importance of infant nutrition and placed the physician caring for children in a central position. The first is the general interest on the part of the public in food and nutrition. The second is the concept of "imprinting" or inducing changes during early life that program future development and result in permanent patterns in the adult.

Interest in food and nutrition has created widespread awareness about the foods we eat, the caloric content of those foods and the concentration of macro and micronutrients contained therein. This has resulted in regulations mandating nutrient labeling and restricting misleading advertising of foods. Certainly this new interest has great importance in pediatrics. Mothers are genuinely concerned about what they feed their children. This concern, properly harnessed by the knowledgable physician, can result in developing good eating habits at an early age.

Perhaps more important from the standpoint of the young infant is the concept of imprinting. We now know that the early environment can cause changes in normal growth and development whose marks are left throughout life. An important factor in this early environment is the state of nutrition. For example, caloric intake during the early growing period, while cells in various organs are still dividing, can alter the rate of cell division and result in an organ with fewer or greater than the expected number of cells. Thus severe undernutrition may result in retarded cell division in brain and subsequently in a brain with a reduced number of cells. Conversely, overnutrition, especially excess caloric intake, may result in accelerated cell division in adipose tissue and in a permanently hypercellular adipose depot. This is associated in adult life with an extremely refractory kind of obesity. Less well studied, but perhaps of even greater health significance, is the relation between later atherosclerosis and early ingestion of cholesterol and saturated fat. What we know so far is that even in young adults found to have died of other causes moderate fatty streaking and plaque formation can be found in arterial walls. Since high amounts of cholesterol and saturated fat in the diet is one major risk factor in atherosclerotic heart disease, concern has been mounting that the amount of these substances in the infant diet might in some way influence the later development of coronary heart disease.

Hence the well-trained physician must be concerned not only with the quantity but with the quality of the infant diet. He must recommend a feeding pattern that takes into account the latest thinking in the areas of caloric requirement,

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percent of macronutrients and amounts of micronutrients. Since requirements will vary at different ages he must be aware of the dynamics of change as the infant grows.

NUTRIENT REQUIREMENTS DURING THE FIRST YEAR OF LIFE

The most accurate index of adequate nutrition during the first year of life is "normal growth." Growth is more sensitive than any other parameter to the total caloric and amino acid requirements of an infant. But what is normal growth? This seemingly obvious question has not been answered in an entirely satisfactory manner. Most pediatricians use as their standard of reference a set of height and weight curves derived from observing a group of Iowa children or Boston children eating a "normal" diet. Thus we take as optimal growth a standard that really represents average growth at a given point in time, under a given pattern of food intake. We then modify the diet of the infant to fit that reference.

If we admit that we cannot by any known means derive a figure which will establish the optimal rate of growth, and if we then decide that over the centuries nature has evolved what is at least an optimal rate for survival, then our standard would best be the growth rate of infants who are receiving almost their entire caloric intake from breast milk during the first year of life. The composition of human breast milk is shown in Table 1.

Table 1. Percent of Nutrients in Human Milk

% Total Solids	% Fat	% Casein	% Whey Protein	% Lactose	% Ash
12.4	3.8	0.4	0.6	7.0	0.2

Human milk contains about 0.66 calories per cc or about 20 calories per ounce. These calories are apportioned so that 6 percent come from protein, 56 percent from fat and 38 percent from carbohydrate. Based on these figures and measurements of the average range of intake of human milk by infants of various weights and ages, growth curves can be constructed and macronutrient requirements recommended. Table 2 sets forth the recommended Daily Dietary Allowances (RDA) for infants 0 - 0.5 years, 0.5 - 1.0 years and 1 - 3 years.

Table 2. Recommended Daily Dietary Allowances (RDA)*

Nutrient	Age (years) 0-0.5	0.5-1.0	1-3
Energy (kcal)	117/kg	108/kg	1,300
Protein (gm)	2.2/kg	2.0/kg	23
Vitamin A (IU)	1,400	2,000	2,000
Vitamin D (IU)	400	400	400
Vitamin E (IU)	4	5	7
Ascorbic acid (mg)	35	35	40
Folacin (µg)	50	50	100
Niacin (mg)	5	8	9
Riboflavin (mg)	0.4	0.6	0.8
Thiamin (mg)	0.3	0.5	0.7
Vitamin B_6 (mg)	0.3	0.4	0.6
Vitamin B_{12} (µg)	0.3	0.3	1.0
Calcium (mg)	360	540	800
Phosphorus (mg)	240	400	800
Iodine (µg)	35	45	60
Iron (mg)	10	15	15
Magnesium (mg)	60	70	150
Zinc (mg)	3	5	10

*The Recommended Dietary Allowances are the levels of intake of essential nutrients considered in the judgment of the Food and Nutrition Board on the basis of available scientific knowledge to be adequate to meet the known nutritional needs of practically all healthy persons. Food and Nutrition Board, NAS-NRC, revised 1974.

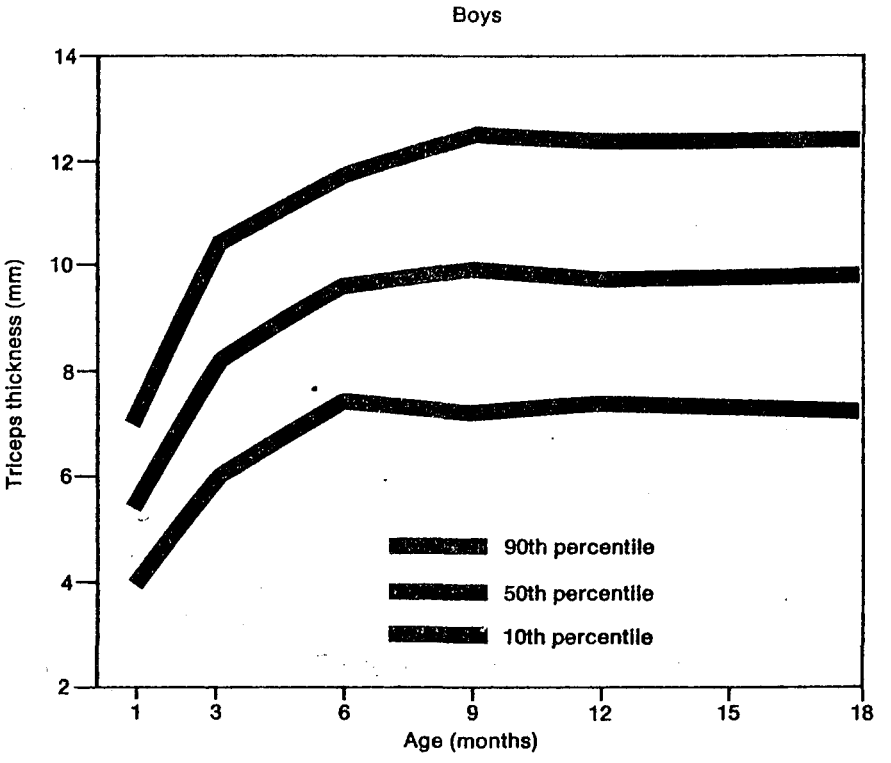
The requirements for protein and energy are listed but how that energy should be derived (the percent fat vs. the percent carbohydrate) is left open. This is an expression more of our lack of knowledge than of our conviction that the source of energy is unimportant.

Requirements for protein assume high quality protein such as the casein or whey proteins usually found in breast milk. Again, nothing more specific is recommended since it is assumed that as long as all the essential amino acids are supplied (nine in the case of the young infant) the source is not important. This may not be entirely true and at present we are beginning to learn that the types of protein may indeed be important and that protein mixtures resembling breast milk may be more efficiently utilized than other protein mixtures.

The requirements for vitamins and minerals have been calculated from the amounts necessary to prevent deficiency symptoms plus a "margin of safety" to cover those infants whose requirements may be higher. Again the method of setting these RDAs is imprecise and although it is perhaps the best "educated guess" at the time the standards are being set, these allowances are constantly being revised as new information becomes available. This method of arriving at Recommended Daily Allowances has been criticized by certain groups, particularly a segment of the population believing in higher requirements for vitamins and minerals. These groups assume that the requirements for optimal health may be different from those necessary to prevent deficiency symptoms and that the "margin of safety" is not nearly enough. There may very well be a certain amount of truth in these criticisms but the problem is that we do not know how to define optimal health and that we do know that excess amounts of certain vitamins and minerals can be extremely toxic. This is particularly true with vitamins A and D and with calcium, phosphorous and iodine. Until a more precise method of determining the optimal amount of each nutrient required evolves, the present system, though imperfect, seems to be the best available. However the physician should be aware of its shortcomings and should utilize new information as it appears. Certain information that will necessitate changes and additions to the RDAs is already available. For example, essential fatty acid deficiency in infancy is now well recognized and hence requirements for essential fatty acids will have to be set. From a practical standpoint this means that a certain amount of fat of mixed composition is necessary for optimal growth and development. Totally skimmed milk for an infant not receiving fat from other sources is, therefore, inappropriate.

ASSESSMENT OF NUTRITIONAL STATUS

So far we have talked of growth as an increase in length and weight. We have paid little attention to the actual composition of the weight being deposited. Recently we have been becoming more and more aware of the importance of body composition in assessing whether an infant is growing properly and hence whether his nutrition is adequate. Standards of weight for height can be calculated from the weight and height curves. These should be used much more than they are. Such ratios are extremely important in suggesting whether the infant is depositing too much or too little fat tissue. Fat deposition can actually be measured more directly by using calipers and measuring triceps or subscapular skinfold thickness. Figure 1 shows curves derived from such measurements for boys and girls during the first 18 months of life.



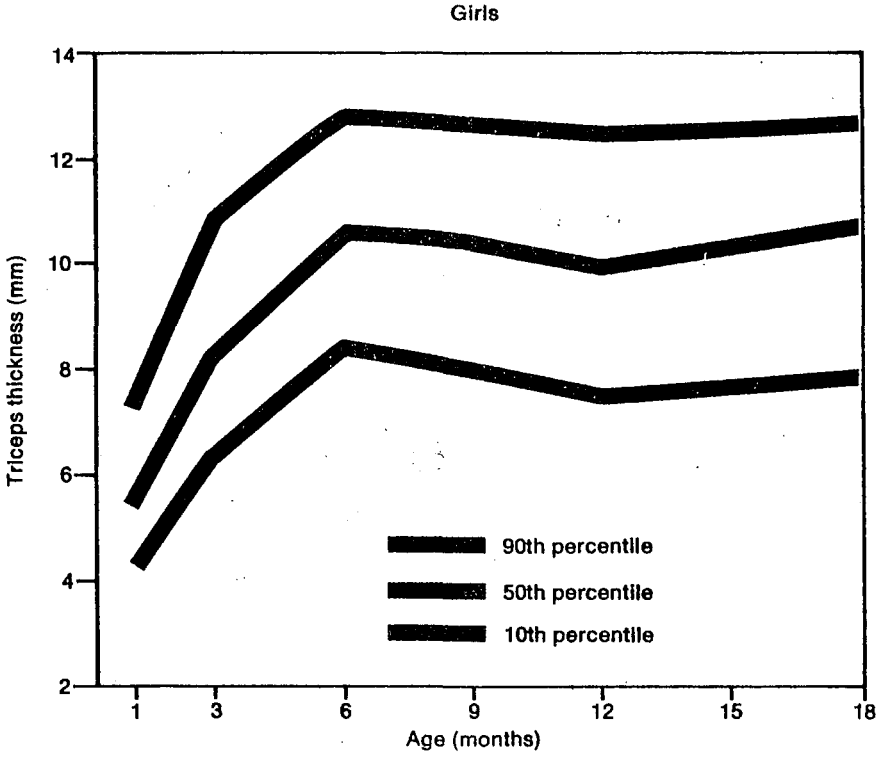


Fig 1 Triceps skin-fold thickness during first 18 months of life. Data are from a longitudinal study of Swedish children (122 boys and 90 girls) in an urban community.

I believe these measurements should become a routine part of the infant's physical examination, as routine as length, weight and head circumference. They are relatively easy to do and a well-trained physician's assistant or office nurse can perform them accurately.

With a combination of careful dietary history and growth measurements it is not difficult to determine whether the requirements for energy and protein are being met. Certain of the micronutrients require measurements other than growth to determine adequacy. Iron is particularly important in this respect, since iron deficiency anemia is very common during infancy. It is especially common if the child is growing rapidly because during such times blood volume is expanding at its greatest rate and hence new hemoglobin is being synthesized, requiring increased availability of iron. Although breast milk has more iron in it than cow's milk or unfortified formula, none of these foods is a good source of iron. For this reason determination of iron status is an important part of the physician's responsibility. It is most simply determined by measuring hemoglobin or hematocrit concentrations several times during the first two years of life. While precise normal values are not agreed upon by all experts, certainly a hemoglobin below 11 gms after the first few weeks of life is unacceptable. Any child who has had hemolytic disease during the neonatal period or who was premature at birth is particularly sensitive to developing subsequent iron deficiency anemia. Such children should be monitored extremely carefully and as we shall see their diets should be routinely supplemented with iron.

During the past few years, a number of pediatricians have begun to monitor the level of cholesterol in all of their patients. This procedure will identify those infants with a tendency to high values either for genetic reasons or because of a hyperresponse to exogenous cholesterol. Such infants can be placed on diets with lowered amounts of cholesterol and generally serum values will fall. As we can see, assessment of nutritional status is not terribly difficult and if it becomes a routine part of infant care could contribute to a rational approach to infant feeding. Table 3 outlines the ways in which a physician can efficiently determine his patient's nutritional status.

Table 3.

History - type of formula, amount consumed or time spent on nursing; other foods consumed especially those high in saturated fat or low in iron.
Anthropomorphic Measurements - all visits; height, weight, head circumference, triceps, fat fold thickness.
Laboratory - hemoglobin, hematocrit and serum cholesterol at three months and one year.

DIETARY MANAGEMENT

Essentially two major considerations must be decided upon in the dietary management of a normal young infant. (1) Whether to breast feed or bottle feed. (2) When and how to introduce solid foods. The first decision should be made before the infant is born so that the mother can be prepared for the initial feedings.

As I have pointed out breast milk has been the natural method for infant feeding throughout the ages. All mammals breast feed and the composition of their breast milk has evolved in such a manner as to be highly individualized to meet the needs of both the infant and the mother of a particular species. The process of lactation is one during which a number of changes occur, beginning in late pregnancy and culminating in the synthesis and secretion of milk. We are not aware of the long term consequences to the mother of artificially shutting off these mechanisms after the infant is born. For example the nursing period places major nutritional demands on the mother. These demands are much greater than those during pregnancy. To prepare for this all mammals, including the human, deposit fat tissue around deep organs during pregnancy to be utilized during lactation. The average mother will deposit 2 - 4kg (5 - 10 pounds) of fat in this manner. Thus from a practical standpoint, weight loss after pregnancy to reach prepregnancy weight is much more difficult if a mother is not breast feeding. The breast feeding mother will gradually consume the excess fat during the metabolic processes involved in milk synthesis.

Human breast milk is highly adapted for the human infant. It is an almost complete source of all required nutrients and infants will grow adequately on breast milk alone for the first six months of life. Human milk is relatively low protein milk, containing approximately one fourth the concentration of protein in cow's milk and one tenth to one fifteenth the protein content of milk of certain carnivores such as the fox and the dog. This is due to the relatively slow rate of growth of the human infant during the nursing period when compared to these other species. By contrast human milk contains approximately the same fat content as cow's milk and somewhat more carbohydrate in the form of lactose than cow's milk. In addition the kind of protein found in human milk differs considerably from that found in cow's milk. The latter is almost entirely casein whereas the former is made up of equal amounts of casein and whey protein, which is mainly lactoglobulin. This is no doubt related to the ability of the gastrointestinal tract of the human infant and the young calf to handle these particular proteins. Although infant formulas that will simulate human milk can be constructed, they do not duplicate the actual composition of the protein or the fat present in human milk.

Human milk is rich in certain other nutrients required by the growing infant. For example, the average liter of human milk contains 43 mg of vitamin C in comparison to about 20 mg in a liter of cow's milk. With the exception perhaps of iron, vitamin A and vitamin D, the young infant's dietary requirements are met by breast milk in a form that is most efficient for his body to absorb and utilize.

Breast milk offers advantages other than those based on nutrient content. The placentas of certain mammals will allow passage of the immunoglobulin IGg during late gestation. In those mammals, including the human, the milk contains very little IGg and IGA is the predominant form of antibody found in both colostrum and milk. By contrast, those mammals such as the cow, who do not transmit IGg, have IGg as the predominant antibody type in their milk. Again we can see pregnancy and lactation acting as a continuum in preparing the infant for external survival. The IGA in human milk probably offers protection at the surface of the gastrointestinal tract from bacterial invasion. In addition to antibody human milk transmits maternal macrophages, capable of producing antibody and programmed into the material immune system, offering the infant protection from a variety of infections.

A final advantage of breast feeding is that the quantity taken in is controlled by the infant's satiety mechanisms rather than being determined by a pre-existing figure in the mother's mind. It has been demonstrated recently that bottle fed babies, consuming a formula of identical caloric content to human milk, gain more weight during the first year of life. This is no doubt due to the mother's desire to drain the bottle dry. In view of our concern about the early genesis of obesity this increased weight gain may not be desirable.

The major advantage of bottle feeding is convenience. I am not sure why it was more convenient to carefully mix a number of constituents and prepare a series of sterile formulas than to put a child to the breast. I am not even sure why the "modern" infant formula preparations are more "convenient" than breast feeding. How this notion took hold is difficult to understand but it is extremely prevalent in our population. This can be appreciated simply by noting that 80 percent of our population never breast feeds and 95 percent do not breast feed beyond three months of age. Thus formula feeding has become the rule rather than the exception and the physician, while attempting to change this trend, must be able to counsel the mother for efficient formula feeding. If evaporated milk is used it must be suitably diluted to reduce the content of total solids and the caloric density as well as the content of protein. In order to bring the protein concentration into the range of breast milk, caloric density will be lowered too much. Hence carbohydrate, usually in the form of dextro-maltose, is added to reach the desired calorie concentration of 20 calories per ounce. Commercially prepared formulas have already done all of this and one simply adds water or gives the formula which comes "ready to feed." In the case of the prepared formulas the source of carbohydrate is lactose, the same as in breast milk. The source of protein is casein, prepared from cow's milk, and the fat content is more unsaturated and lower in cholesterol than the fat in human milk. Most prepared formulas are fortified with RDAs for most nutrients and many even contain added iron. Thus, although not reproducing human milk in all particulars (primarily in the type of protein and fat), prepared formulas have been shown to supply an adequate total source of nutrition during early life. The major problem that must be impressed on the mother is that the feeding of any formula from a bottle will provide the temptation to overfeed. This should be discouraged. Another practice to discourage is propping the bottle into the infant's mouth and allowing him to suck himself to sleep. This exposes the erupting teeth to relatively high carbohydrate concentrations and may set up the conditions for developing dental caries.

The introduction of solid foods normally constitutes the beginning of the weaning period. It normally constitutes a prolonged process by which the infant goes through a smooth transition from breast feeding to the family's regular diet. This is usually begun gradually in the second six months of life. The trend toward artificial feeding of infants has brought with it a trend for earlier and earlier introduction of solid foods. In a study in this country it was found that by one month of age 67 percent of infants were taking solid foods and by two months 96 percent were already on solid foods. In general the feeding of solid foods has not been as a replacement for formula but has been in addition to formula, resulting in an increase in calories consumed. In a recent British study it was found that mean energy intake at 6 weeks of age was 135 kcal/kg and that weight gain was excessive. Data from other studies reveal that most infants in the United States by three months of age are consuming an excess of almost all nutrients.

Figure 2 demonstrates these findings. The marked excessive increase in iron intake is no doubt due to iron supplementation which is common at this time.

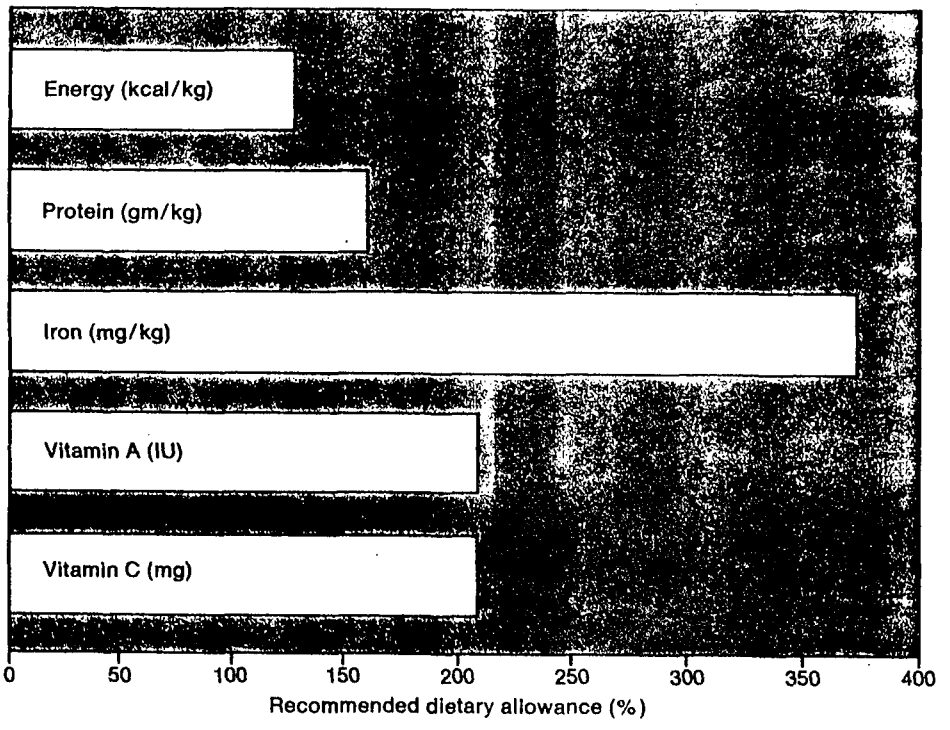


Fig. 2 Mean reported nutrient intakes at mean age 2.28 months and mean weight 5.28 kg. Iron is expressed as percent of recommendation of American Academy of Pediatrics Committee on Nutrition.

Given the tendency to consume excess calories and other nutrients, early introduction of solid foods, especially those of high caloric density should be discouraged. I see no real need for solid foods before four months of age and I find no data to convince me that introducing solid foods will placate a "fussy" infant. At four months solid foods can be introduced slowly as a replacement for breast milk or formula. The caloric density and nutrient content of the particular foods should be known so that their contribution to the total dietary intake can be quantitated. At this age it makes no difference whether commercially or home prepared weaning foods are used. Since iron is often in low supply if the infant's diet is not being supplemented, fortified cereals might be the first solid food introduced. If serum cholesterol levels are high, foods rich in cholesterol, primarily eggs, may be deferred until later.

CONCLUSIONS

Infant nutrition is becoming more and more important as we learn that feeding practices during early development may permanently affect subsequent health and well-being. In addition public awareness has made mothers more concerned with proper infant nutrition. Physicians can utilize this awareness to promote sound nutritional principles. However, this can be done only if the physician is aware of certain nutritional considerations and if he considers adequate nutrition important enough to supplement his usual office examination with a nutritional history and the introduction of certain measurements designed to monitor nutritional status. By following these parameters and giving sound nutritional advice, the physician can often avert such later problems as iron deficiency anemia, early onset obesity and perhaps even early atherosclerosis.

Breast feeding should be encouraged because of its advantages to both mother and infant. If formula feeding is used care not to overfeed should be taken and bottle propping discouraged. Introduction of solid foods should be delayed until about age four months and then the solid foods should be used as a replacement for rather than in addition to formula.

THE INFLUENCE OF MATERNAL NUTRITION ON THE CELLULAR GROWTH OF THE PLACENTA AND THE FETUS

Pedro Rosso, M.D.*

The fact that growth occurs by increase in cell number and by increase in cell size has been known for many years. However, the method used to quantitate this phenomenon and to determine its timing were made available only in the late 1950s and early 1960s.

Since the content of deoxyribonucleic acid (DNA) is constant per diploid nucleus it may be used as a measure of cell number (5, 6). Once the number of cells has been determined, the average cell size may be obtained by relating the protein content of the organ to the DNA content (protein/DNA ratio). The use of these parameters is based on certain assumptions. For example, the content of interstitial tissues, such as collagen, and the occurence of polyploidy are considered to be minimal in most organs. In addition, polyploidy is expected to be associated with a commensurate increase of cytoplasm. Histological evidence supports the validity of these assumptions in several tissues (20, 15, 43). In brain, for example, except for few tetraploid cells in the cerebellum and cerebral cortex, all the cells are diploid (30). Further, recent evidence has challenged the existence of polyploidy in these regions (21). In liver the existence of ploidy is recognized. However, it has been shown that as ploidy increases the cytoplasmic mass of the cells increases proportionally. Thus a tetraploid liver cell has twice as much cytoplasm as a diploid cell (20). Certain other tissues, such as skeletal muscle and pancreas, contain a significant proportion of multinuclear cells (19). In these organs an increase in DNA content represents an increase in nuclear number and not an increase in the actual number of cells. If it is assumed that for each nucleus there is a discrete, though not bounded, cytoplasmic mass, then the same principles may be employed. Finally in organs that have a syncitium as a main component, such as placenta, again the same principle is operable if each nucleus maintains the same amount of cytoplasm.

Thus, regardless of whether the absolute cell number or cell size is calculated, the hypothesis that increase in total organ DNA represents an increase in the number of cells and that an increase in protein/DNA ratio represents an increase in cytoplasmic mass would appear to be valid. Further, the quantitative expression of any substance, such as mgr of ribonucleic acid (RNA), mEq of K+, or units of enzyme activity per DNA would reflect the average cell content of the substance.

By using DNA and protein/DNA ratio as parameters, it has been shown in the rat that growth proceeds through a sequence of three phases (18, 45). In the first phase increments in body size are caused entirely by cell division. DNA content of the organs, weight, and protein content increase proportionally, reflecting a constant cell size. In the second phase the rate of DNA synthesis, and therefore

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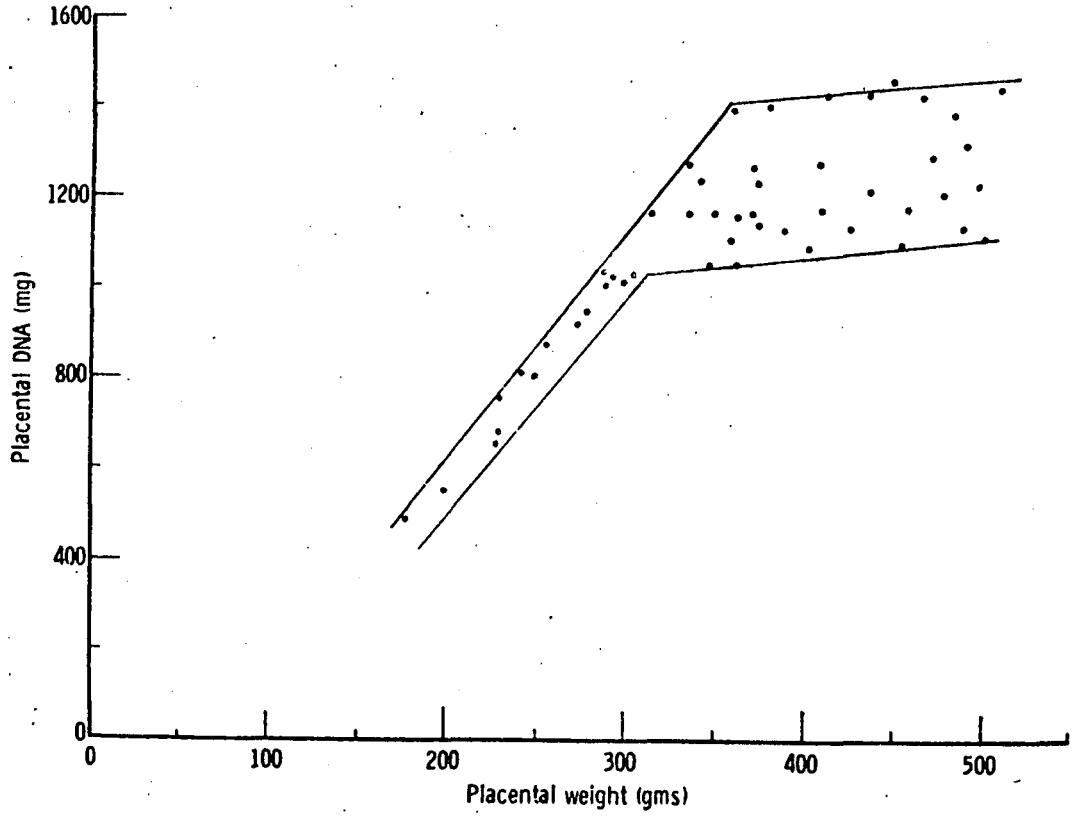
of cell division, decreases at different times for different organs. Weight of the organs and protein content continue their linear increment, which results in an increased protein/DNA ratio. Thus in the second phase while some cells are still dividing, others are increasing their size. Finally, during the third phase, cell division ceases completely in some organs while in others it reaches a steady state with cell loss. Thus growth continues in this phase because cells are getting larger. Finally, protein synthesis slows down and reaches a balance with the rate of protein catabolism. Normally no further increments in cell size will take place after this stage, and the organism is considered to have attained maturity. In the rat, where growth has been studied from early prenatal stages until maturity, these phases do not have well-defined limits but merge gradually one into the other. The time when cells are actively proliferating varies considerably from organ to organ, each completing this phase of growth at a specific time.

Normal Placental Growth

Study of the cellular growth of the placenta has received increasing attention in recent years. Normal placental growth was studied first in the rat and subsequently in the human, the sheep and the rhesus monkey (46, 48, 28, 24).

In the rat, placental weight increases linearly until approximately day 20 of gestation (length of pregnancy in the rat is 21 days) and then falls off slightly. Protein and RNA content also continue to increase until term, whereas DNA fails to increase after the seventeenth day of gestation (46). The leveling off of placental DNA content at this time reflects cessation of DNA synthesis. This interpretation is supported by radioautographic and 14C-thymidine incorporation studies (26, 46). Hence in rat, placenta cell division stops around the seventeenth day and the rest of the growth is due to an increase in protoplasmic elements without further cell division. Thus, just as in other organs of the rat, three phases of cellular growth may be described in placenta. From the tenth day until about the sixteenth day of gestation DNA synthesis and net protein synthesis are proportional and cell number increases whereas cell size is unchanged. This is the hyperplastic or proliferative phase of placental growth. From the sixteenth to the eighteenth day the rate of cell division slows down while protein accumulation continues; thus hyperplasia and hypertrophy are occuring together. Finally around the seventeenth day cell division stops altogether while weight and protein still continue to increase. The protein/DNA ratio increases markedly, indicating that cell size increment, or hypertrophy, is the major mechanism for placental growth at this time. Although the exact timing of events is not so clear as with rats, available data indicate that human placenta grows in a qualitatively similar manner. Weight, protein and RNA content increase until term. DNA, however, ceases to increase after the placenta reaches about 300 g. This corresponds to a fetal weight of about 2400 g or a gestational age of 34 to 36 weeks. Thus, as demonstrated in the rat, cell division also ceases before term in human placenta (48). This would indicate that a constant number of placental cells sustain the steep increase in fetal weight of the last weeks of pregnancy (Figure 1).

Figure 1. - DNA content of human placenta versus placental weight (48).



In vitro studies have demonstrated that after week 34 of pregnancy there is a shift in the pathway of glucose metabolism away from the hexose monophosphate shunt. This finding is consistent with a reduction in nucleic acid synthesis, thus supporting the evidence that DNA synthesis ceases at this time (2).

Sheep placenta has a pattern of growth comparable to rat and human placenta (28). However, in rhesus monkey, total placental DNA content continues to increase until term (24). There are other significant differences between human placental cellular growth and that of the rhesus monkey. For example, placental RNA content in the macaque increases linearly until term but the slope of the curve is not as steep as with DNA (24). Thus, while in human and rat placenta the RNA/DNA ratio increases during the last half of pregnancy, in the rhesus monkeys it decreases. In contrast, the protein/DNA ratio seems to increase proportionally in both species.

The disproportion between cell number and protein content in the placenta of the macaque is hard to interpret. According to current concepts, this finding would suggest that as pregnancy progresses RNA becomes more efficient in synthesizing protein and therefore proportionally less RNA per cell is able to maintain the same rate of protein cytoplasmic accumulation.

Normal Fetal Growth

Information on human fetal growth, based on the change of weight of the body and of different organs, is extensive. In contrast only a limited amount of information is available on the characteristics of prenatal cellular growth.

The organ whose prenatal growth has been most extensively studied is brain and its different regions. Available data show that DNA content of the whole brain increases linearly until birth and continues to increase at a slower rate during the first few months of postnatal life. The main regions of the brain follow this general growth pattern (16).

The curve for DNA content in fetal brain shows two different slopes with the steeper one up to 20 weeks of gestation. The interpretation of the authors is that the first peak corresponds to neuronal division. Therefore, the bulk of DNA increments during late gestation, and postnatally, would represent glial proliferation (16). (Figure 2).

Changes in brain weight and protein content compared with DNA content reflects the different phases of cellular growth. In human brain both total DNA and protein increase linearly before and several years after birth, indicating that hypertrophic growth of this occurs mainly postnatally (51, 17).

Prenatal cellular growth of the cerebrum in the rhesus monkey is remarkably similar to that in humans. However cerebellum has a proportionally faster prenatal rate of cell division in the monkey (11). Other parameters, such as increase in cerebral cholesterol concentration (a parameter of myelination) are also similar in man and monkey, suggesting that some primates may provide valuable models for a better understanding of normal and abnormal events of human brain growth (11).

Since during prenatal life brain growth is mainly proliferative, increases in DNA content are proportional to protein content and to weight changes. Increase in brain weight, in turn, is reflected in increase in head circumference. This relationship determines a linear correlation between brain DNA content and head circumference during gestation and the first year of life. Thus, DNA content of a fetal brain can be calculated, with an acceptable degree of accuracy, from head circumference (53). A similar relationship of total brain DNA to head circumference also exists in the rhesus monkey, but is best fitted by a quadratic expression (25).

Human cellular growth patterns have also been studied in sixteen organs other than brain during normal fetal development (54). However, there are growth curves available only for heart, liver, kidney and gastrocnemius muscles (44). In all these organs there is a marked linear increase in DNA content that is faster between 13 and 25 weeks of gestation than at later ages. Up to 25 weeks of gestation DNA content of each organ approximately doubles every week. In kidney and heart the protein/DNA ratio increases slowly up to 30 weeks of intrauterine life and rapidly thereafter (Figures 3 and 4). In contrast, protein/DNA ratio in liver

Figure 2.- a) Total DNA-P in the forebrain, from 10 gestational weeks to 4 postnatal months, showing the two-phase characteristics of prenatal cell multiplication. b) A semilogarithmic plot of the data appearing in (a) to show the comparatively sharp separation of the two phases at 18 gestational weeks. Repression lines with 95% confidence limits are added. (Reprinted from Dobbing, J. and Sands, J. Arch. Dis, Childh. 48:757. 1973 with the permission of the Editor).

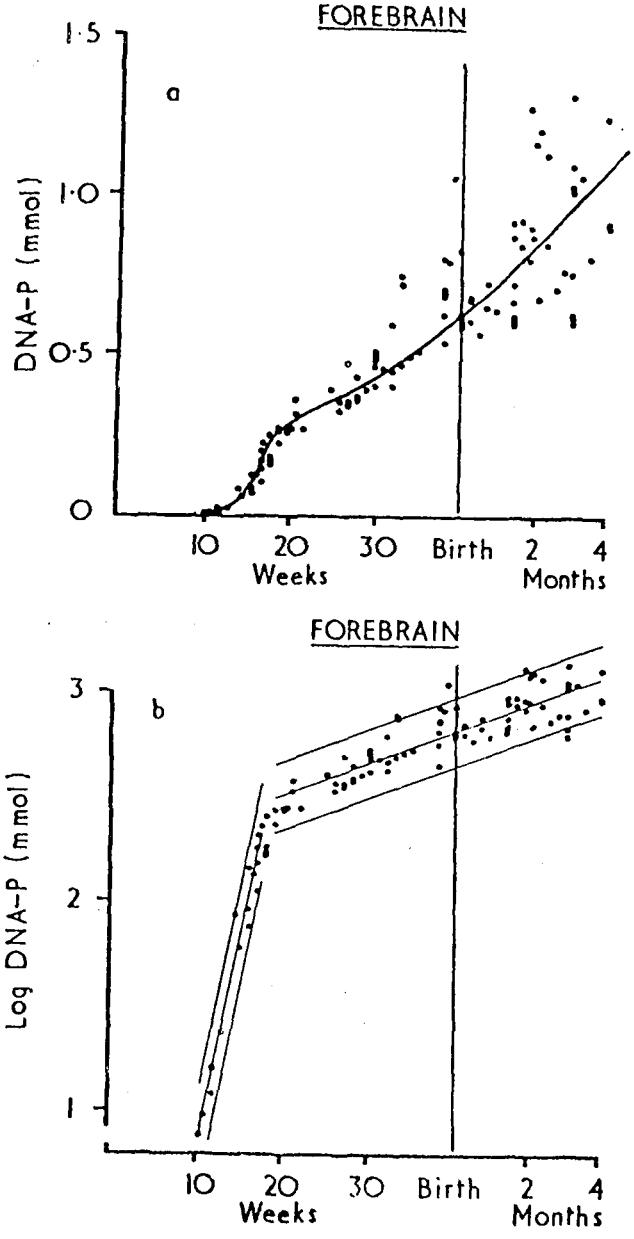


Figure 3.- Total DNA and protein/DNA ratio in the kidneys of human fetuses and newborn of 13 to 42 weeks of gestational age. (Adapted from Widdowson, E., Crabb, D.E. and Milner, R.D.G.; Arch. Dis Childh.; 47:652, 1972).

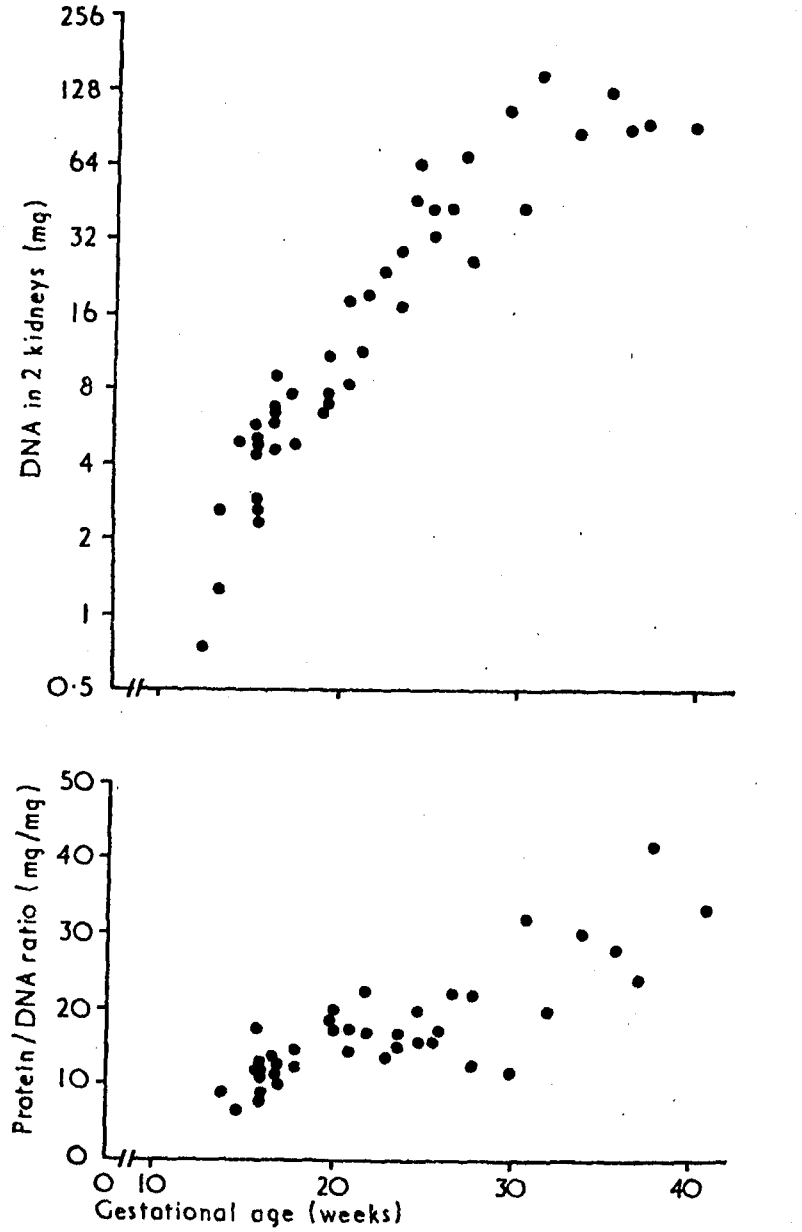
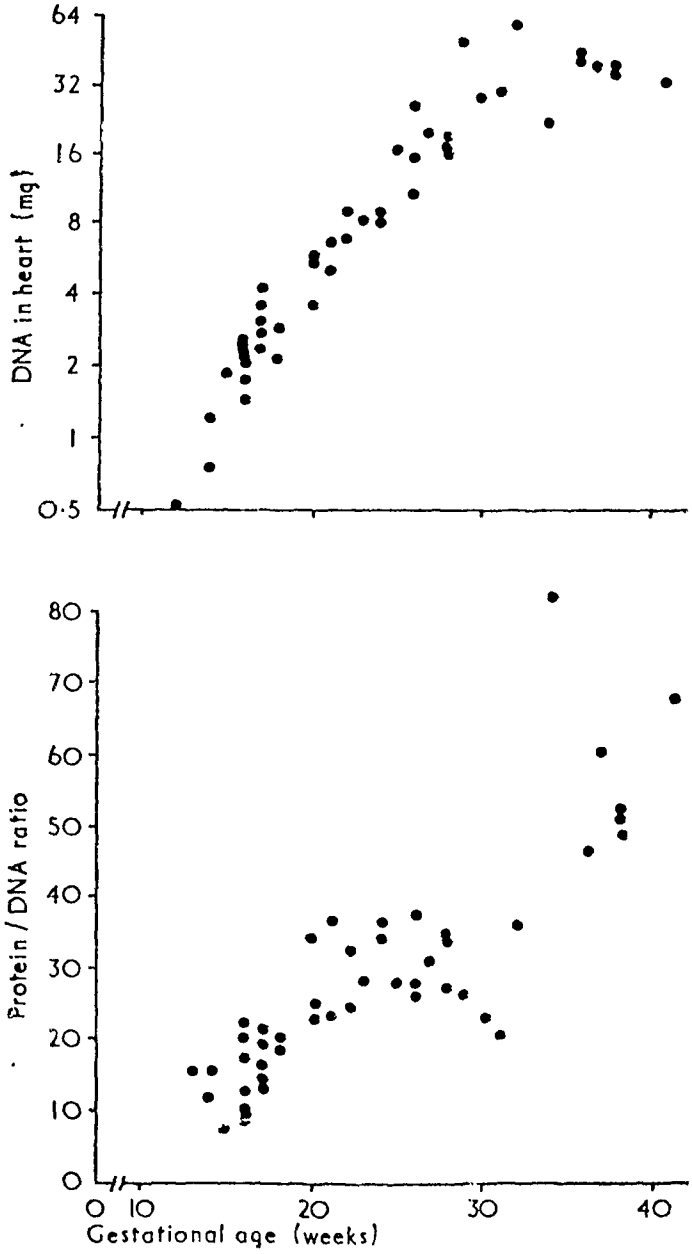
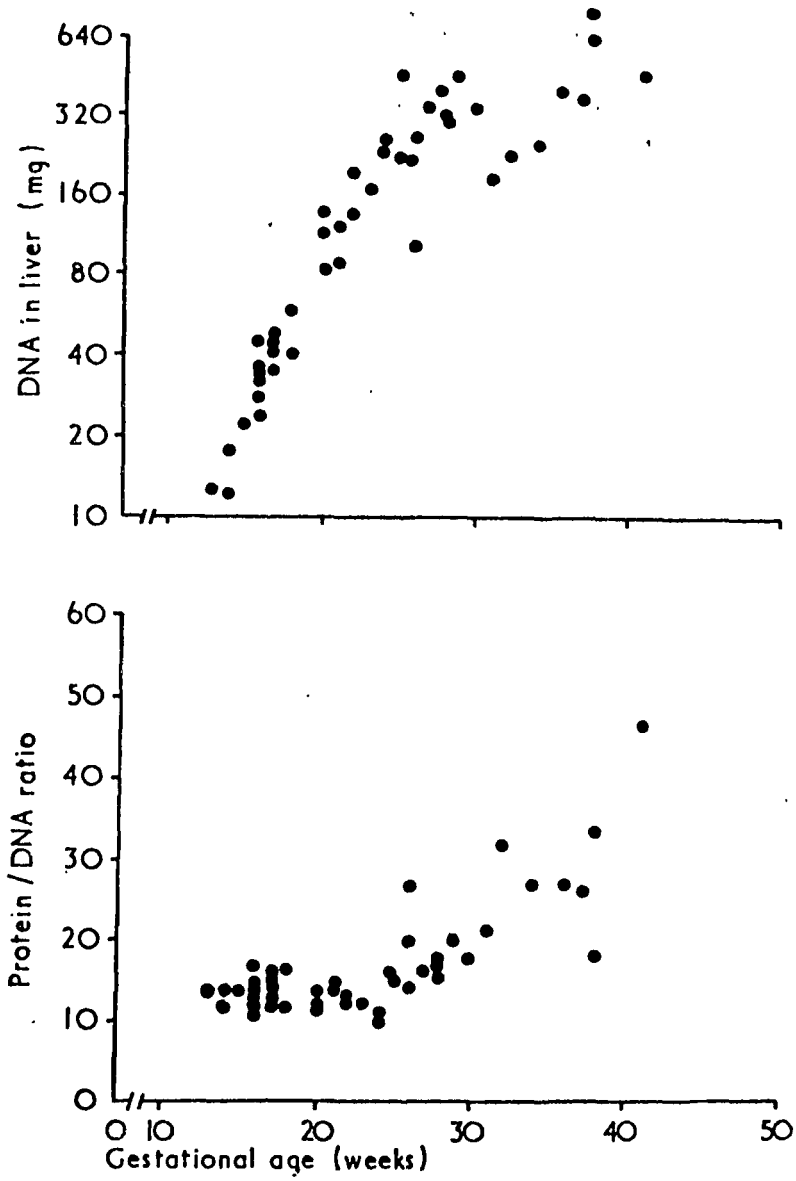


Figure 4.- Total DNA and protein/DNA ratio in the heart of human fetusis and newborn of 13 to 42 weeks of gestational age. (Source as in Fig. 3).



remains almost constant throughout gestation (Figure 5).

Figure 5. - Total DNA and protein/DNA ratio in the liver of human fetuses and newborn of 13 to 42 weeks of gestational age. (Source as in Fig. 3).



The differences in protein/DNA ratio in these organs reflect diversities of timing for the different phases of cellular growth. The combination of simultaneous proliferative and hypertrophic growth in different organs found in the human fetus has also been described in the monkey, suggesting that this may be a characteristic of the primates (11). In the rat, prenatal growth is almost exclusively hyperplastic (45). Growth of muscle, as reflected by changes in DNA content of the gastrocnemii, also increases more rapidly before the 25th week of gestation than thereafter. Protein/DNA ratio doubles between week 15 and 30 and triples during the last week of gestation. No data are available for prenatal human growth or changes in the total muscle mass of the body. In rhesus monkey the percentage of body weight represented by skeletal muscle has been determined by careful dissection of the muscle. It was found that during the entire intrauterine life and until 4 days postnatally skeletal muscle accounted for 20 to 25 percent of body weight (3). In the macaque there is good agreement between the values of DNA content and protein content in various muscles. If the same relationship holds in the human fetus, data from gastrocnemii would reflect changes in total muscle mass.

Nutrient Restriction and Cell Growth

Current concepts of the effect of nutrient restriction on cellular growth are largely based on studies done in the rat. The most common method employed in altering early postnatal nutritional status of rats is to vary the number of pups nursing from a single mother. The average rat litter consists of 10 pups. Malnutrition is imposed by increasing the size of the nursing group to 18 animals and overnutrition by decreasing the size to 3-4. By employing the large litter technique it was demonstrated that at weaning undernourished animals have a smaller body size and a reduced DNA and protein content in every organ (47). Protein/DNA ratio, however, is not affected. These findings suggest that undernutrition interferes with cell division and determines a deficit in cell number without affecting cell size. If these animals are rehabilitated by giving them ad libitum amount of a normal diet they fail to recover completely both their deficit in body size and their deficit in cell number. Cell size, however, reaches normal limits.

Older, although still growing rats, kept for a certain period of time on a restricted diet also have a significant deficit in body weight at the end of the period of restriction. Analysis of DNA and protein content has shown however, that only cell size is affected, with no associated deficit in cell number. After nutritional rehabilitation the deficit in cell size disappears (47).

These results suggest that growth retardation induced by undernutrition may be of two types depending on age at onset and, therefore, on the phase of cellular growth of the animal. If at the time of onset the animal is in the phase of proliferative growth, undernutrition may induce a permanent deficit in cell number. Conversely, undernutrition during the hypertrophic phase produces only a reversible interference with cell size increase.

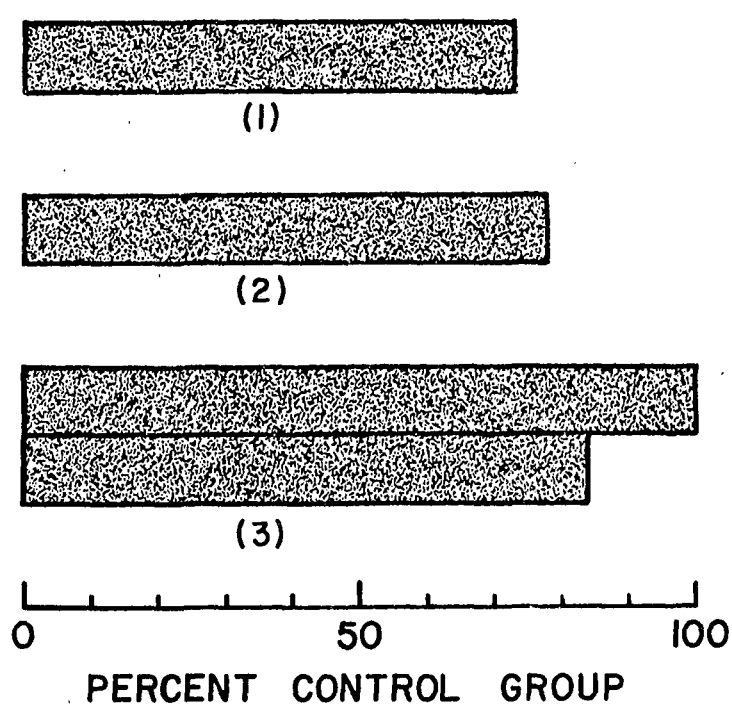
Other evidence has demonstrated that other stimuli able to interfere with cellular growth, such as an overdose of cortisone or lack of growth hormone, will determine a permanent deficit if applied with adequate intensity and/or for a certain length of time (49, 50). Thus, the phase of hyperplastic growth can be considered to be a "critical period".

Maternal Malnutrition and Placental Growth

Rats fed a low protein diet from day 6 of pregnancy have smaller placentas at term, with a 25 percent lower protein and DNA content than placentas from a control group (52). These results suggest that placenta is no exception to the principle that undernutrition interferes with cellular growth and determines a deficit in cell number. Further, since in rat placenta cell division proceeds until day 17 of gestation, the data suggest that the shortage of nutrients reaches a critical level before that day. RNA content in these placentas has been found to be increased at day 13 of gestation. However, another study has demonstrated that at term placentas from protein malnourished rats have a significant reduction in RNA content (37).

Placental DNA content has been found to be significantly reduced in a population of poor women in Guatemala (14). Other studies done in similar populations have also found lower average values for DNA content compared with placentas delivered by women that presumably are better nourished (Figure 7).

Figure 7.- DNA content of placentas from women belonging to low socioeconomic groups. Mean values are expressed as percent of control groups. (Adapted from Dayton, D.H., Filer, L.J. and Canosa, C.: Fed. Proc. 28:488, 1966(1): Laga, E.M., Driscoll, S.G. and Munro, H.N.: Pediatrics 50:33, 1972 (2) and Winick, M. in "Diagnosis and treatment of fetal disorders". Ed. by K. Adamson, New York, Springer Verlag, 1969 p. 83, (3).



However, the difference between groups was not statistically significant (52, 29). The apparent discrepancies between those studies may be explained by factors such as sample size and differences in the nutritional status of the groups being compared. Total protein content has also been reported to be slightly but not significantly decreased in placentas from a malnourished population (29). These results suggest that a moderate degree of maternal undernutrition, probably a caloric deficit, produces only a minor interference with the proliferative and hypertrophic phases of placental growth. Some parameters of RNA metabolism, however, seem to be more affected by a deficit of nutrients than DNA and protein content. For example, polysome/monosome ratio has been found to be 50 percent lower in placentas from malnourished women (29). Polysomes consist of a strand of messenger RNA with ribosomes attached and are the basic units for protein synthesis. Two types of polysomes exist in the cell, those attached to the secretory membrane of the endoplasmic reticulum, or "bound polysomes", and those found free in the cytoplasm, or "free polysomes". For both populations of women the "bound polysomes", presumably involved in the synthesis of protein for export, averaged 21 percent of the total number of ribosomes. This suggests a similar capacity to synthesize peptide hormones.

In spite of the higher percentage of polysomal dissaggregation of the placenta, suggesting a reduced organ capacity to synthesize protein, cell-free protein synthesis per mgr of ribosomal RNA was similar in the malnourished and well nourished women. Thus, when total capacity of the placenta for protein synthesis, obtained by multiplying incorporation per mgr of RNA by RNA content, was compared it was found to be similar in both populations. This finding would suggest that in spite of the reduced polysome/monosome ratio, maternal malnutrition does not reduce the metabolic efficiency of the organ in term of protein synthesis.

Further evidence of abnormal RNA metabolism has been provided by studies demonstrating elevated alkaline ribonuclease activity (RNase) in placentas of malnourished women when compared with a well-nourished population (42). The cellular role of this enzyme is still poorly understood. It has been postulated that it may play a regulatory role for cellular content of RNA. High levels of RNase are usually associated with an increased rate of RNA turnover (22, 33). A low protein diet or dietary restriction has been shown to cause elevation of RNase in liver and brain in the rat (36). A protein-calorie or calorie supplementation during pregnancy has been found to reduce placental levels of RNase activity suggesting that, out of the many variables that may influence placental metabolism, nutrition may have a direct influence on this enzyme (31).

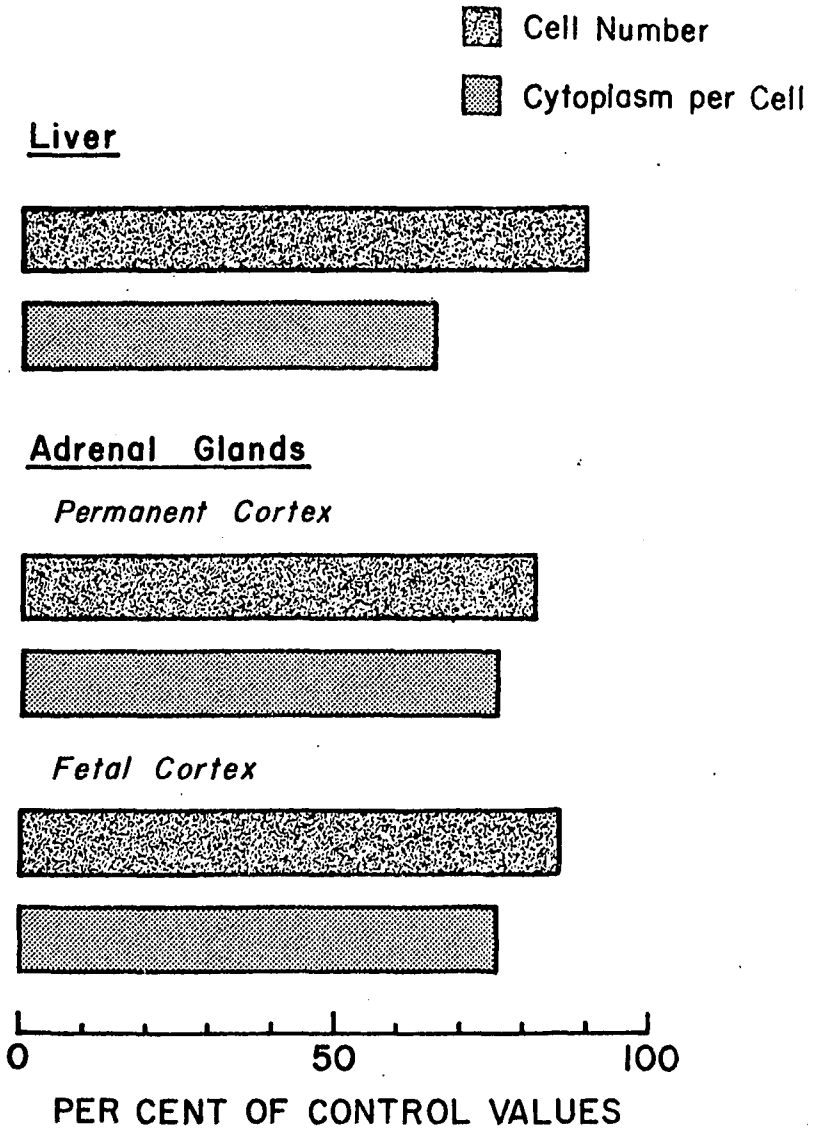
Maternal Malnutrition and Fetal Growth

As discussed elsewhere in this book it is widely recognized that a maternal deficit of calories and/or protein during pregnancy is associated with a reduced birth weight. As indicated by data from the Dutch famine the affected neonates had a small reduction in body length and a 9.6 percent reduction in body weight (40). This would indicate that the fetuses suffered only a minor degree of growth retardation. Other parameters such as head circumference were reduced proportionally to body length.

As discussed in previous sections, a reduction in head circumference probably reflects a proportional decrease in DNA content. Similarly, smaller body segments are likely to reflect an overall reduction in the size of the visceral organs. Based on available knowledge of normal fetal growth and the effects of nutrition

on cell growth this would imply that at term a fetus affected by maternal malnutrition would have a reduced number of cells. Further, based on the characteristics of human prenatal growth no changes in the protein/DNA ratio in some organs, such as liver, would be expected whereas a reduction in both DNA content and protein/DNA ratio in others, such as heart and kidneys, seems likely to occur. Muscle mass probably would show a reduction in cell number and cell size. No data have yet been made available on DNA and protein content of organs of malnourished fetuses to prove or disprove the validity of such speculation. However, by using histological methods of cell counting and direct assessment of cell size, it has been reported that children born from women malnourished during pregnancy have a reduced cell number and reduced cell size in liver and adrenal glands (Figure 7).

Figure 7.- Cell number and cell size in liver and adrenal gland of babies born to malnourished women. (Adapted from Naeye, R.L. Blanc, W. and Paul, C. Pediatrics 52:494, 1973)



No cell counts were made in other organs. However, changes in organ weight demonstrate a 7 to 21 percent reduction, the organ least affected being the spleen and the most affected the adrenals. Average brain weight was reduced 13 percent (32).

It is conceivable that the conditions prevailing during maternal malnutrition may have some common characteristics with those determining a reduced "supply line" to the fetus. This term has been used to characterize a situation in which a reduced maternal placental blood perfusion and/or "placental insufficiency" causes intrauterine growth retardation. Although it is generally assumed that maternal malnutrition causes fetal growth retardation as a direct consequence of the lack of nutrients for the fetus, there are reasons to think that this may be an oversimplification of the problem. For example, it has been recently demonstrated in the rat that during maternal malnutrition there is a reduced transfer of non-metabolizable amino acid into the fetus (35). This may be caused by a reduced capacity of the placenta to transport substances or by a reduced maternal placental blood perfusion. The mechanisms by which uterine blood perfusion is regulated during pregnancy are still unknown but it is conceivable that maternal nutritional status by hormonal mediation, or other mechanisms, may alter blood flow to the conceptus. Thus, it is conceivable that intrauterine growth retardation associated with maternal malnutrition, can be caused by mechanisms similar to those operating during other conditions.

When reduction in the "supply line" occurs early in pregnancy the babies are generally markedly retarded in growth but maintain a normal proportion of their body segments. However, when the onset of the phenomenon occurs later in pregnancy, and probably with a sudden deficit of oxygen associated, the babies appear thin and emaciated and have a marked disproportion between head circumference and body length (34). Maternal malnutrition would cause a proportional growth retardation similar to the first type of small-for-dates babies. Organ analysis of few cases of intrauterine growth retarded babies has shown that brain weight and DNA content are significantly reduced, especially cerebellum (9). The effect in other organs seems to be less clear. For heart, DNA content is lower in growth retarded fetuses compared with controls; however, protein/DNA ratio is similar in both groups. The same trend was found in liver and kidney, although in kidney the reduction in DNA content was considerably greater than in the other organs. No significant changes in DNA content of the gastrocnemii was apparent, while protein/DNA ratio tended to be lower (44). Unfortunately, the two clinical types of intrauterine growth retardation are not widely recognized yet, and therefore it is unknown which type of babies were included in the previous study.

Current knowledge on the effects of maternal nutrition on DNA and protein content of the fetal organ is based on work done in several mammalian species. So far only one of these studies has been done in primates and the work is still in progress. Some preliminary information from such a study has been made available but, since DNA and protein values have been expressed as concentration, it is impossible to draw any conclusion yet on whether DNA content was reduced (10).

In the rat either 50 percent overall reduction of food intake or a decrease in protein content of the diet to 5 or 6 percent throughout pregnancy causes a 25 to 30 percent reduction in birth weight. More moderate restrictions of dietary protein cause a graded effect on birth weight (52, 4, 13, 56).

The decrease of neonatal body weight reflects a reduction in the weight of every organ measured. Although the organ weight reduction is proportional to the reduction of body weight, some organs, such as brain, tend to be proportionally less affected. Most studies show that brain weight is only 15 to 23 percent less than in control animals. By contrast, kidney, spleen and thymus weight tend to be proportionally more reduced than body weight (52, 56, 27). DNA content of the brain in the newborns of protein restricted mothers has been found to be reduced 10 to 15 percent when compared to a control group (52, 55). Autoradiographic studies have shown that by 16 days of age the fetuses from protein restricted mothers have an overall reduction in the rate of cell division in the brain (54). This has been shown to follow a well-defined regional pattern determined by the rate of cell division in different areas of the brain. For example, in areas where at day 16 of gestation the rate of cell division is comparatively slow, such as the cerebral white and grey matter, the number of cells that incorporate labeled thymidine has been found moderately reduced when compared with control fetuses. Areas adjacent to the third ventricle and subiculum, where proportionally more cells are dividing at this age, are found to be proportionally more affected. Finally, the cerebellum and the area adjacent to the lateral ventricle have the most marked reduction in the number of dividing cells when compared with control samples. These results indicate that the brain is not uniformly affected by maternal malnutrition, those areas more susceptible to the effects of nutrient deprivation being those with a higher rate of cell division.

The effect of maternal deprivation on the rest of the organ is still relatively unexplored. Progeny of rats fed a 6 percent casein diet during pregnancy have a reduced DNA content of the kidneys. Histological studies have demonstrated that this deficit reflects a reduction on glomerular cells and fewer collecting ducts. Proximal tubules are also shorter and less convoluted (57).

Studies done in guinea pigs also have shown that a restricted diet from day 35 of gestation results in a reduced brain weight and reduced DNA and protein content (8).

Long-term Effects of Prenatal Nutrient Deficiency

As discussed in preceding sections, the proliferative phase of growth is a critical period, susceptible to permanent deficit. Since maternal malnutrition affects fetal growth by interfering with cell division, the unborn child is at risk of being permanently affected. No data are available on the effects of prenatal undernutrition on subsequent cellular growth in a human population. The indirect evidence, however, as judged by subsequent growth of the babies affected in utero during the Dutch famine, is that there is complete recovery of physical growth and no detectable deficit in mental capacity (40). These results have been interpreted by some as conclusive evidence that maternal malnutrition causes no permanent effects. However in a field like this, with so many facts still unknown, a more cautious interpretation of the data seems advisable. The fact that physical growth does not seem to be affected in this population does not necessarily rule out the possibility that a certain organ or function may be specifically affected. Similarly, an average I.Q. comparable to the general population does not imply absence of some degree of behavioral or emotional disfunctions in those affected by maternal malnutrition. Again, any speculation on this problem must take into consideration the results obtained in animals. In the rat the progeny of mothers fed a protein-restricted diet during pregnancy and subsequently reared in litters of 4 pups by a foster mother, a situation that accelerates growth in a normal animal, have been reported to have a reduced brain weight and DNA content at 21 days of age (58),

and no deficit in either parameter at 6 months of age (41). However, in spite of their subsequent recovery in brain weight and cell number, the progeny of protein-restricted rats have a series of lasting behavioral abnormalities and learning disabilities. These observations have been made in open fields, by introducing abnormal stimuli or observing their interaction with their peers (23, 39, 7, 38).

Long-lasting effects have also been found in kidney. Again, by rearing the pups in litter of 4 animals a partial recovery of DNA content can be obtained. However, the increase in number is restricted to existing nephrons and to a lengthening of the proximal convoluted tubes (1).

Thus, the rat model demonstrated that although the fetally malnourished animal may reach a considerable degree of somatic recovery, certain organs and functions may be permanently affected.

As in other situations, the experimental data in this area are not directly extrapolatable to humans because of interspecies differences. They raise the possibility, however, that in spite of the apparent full recovery reported in humans by epidemological studies, a closer analysis on an individual basis may reveal abnormalities.

Summary

Human placental and fetal growth proceeds through a hyperplastic phase of cell proliferation, characterized by increments in DNA content, and a hypertroplic phase or increase in cell size, characterized by increments in protein/DNA ratios. In placenta the proliferative phase lasts until approximately the 35th week of gestation. In fetal organs, there is a rapid increase in cell number until the 25th week of gestation and a slower increase thereafter. Cell size begins to increase significantly at about 30 weeks. Maternal malnutrition has been shown to interfere with placental cell division and RNA metabolism. Fetal growth is also affected by maternal malnutrition. Histologic evidence demonstrates a reduced cell number and cell size in liver and adrenal glands. Indirect evidence suggests that brain cell number may also be reduced.

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NUTRIENT NEEDS DURING PREGNANCY

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Nutrient needs are increased during pregnancy. The basis of the need for additional nutrients is probably twofold: to provide for the synthesis and deposition of new tissue, and to support the increase in maternal metabolism and fetal metabolism. Even though metabolic adjustments which occur during pregnancy increase the efficiency of utilization of nutrients in the diet, dietary intakes of all nutrients still should be increased for optimal pregnancy outcome.

The Food and Nutrition Board of the National Research Council (NRC) (1) has formulated nutrient recommendations for pregnancy which are judged to be adequate for the maintenance of good nutrition in healthy pregnant women in the United States. These nutrient allowances are generally based on the following information: epidemiological studies of nutrient intake of pregnant women who are healthy, summations of nutrient deposition in tissue gained during pregnancy, data from balance studies where intake is compared to nutrient output, and comparison of intakes to biochemical and clinical parameters related to nutritional status. Using this information, the Food and Nutrition Board recommended an increased increment for pregnancy. Diet recommendations for adult women can be made by adding this increment to the recommendations for nonpregnant women; (Table 1). Allowances for pregnant adolescents can be estimated by adding the increment to the NRC allowance for nonpregnant teenagers fifteen to eighteen years of age (Table 1).

In this paper the basis of the protein, energy, and iron recommendations will be discussed. A zinc recommenation was made for the first time in 1974 and the basis of this recommendation will also be presented. Particular emphasis will be given to the needs of the pregnant adolescent throughout the paper.

THE UNIQUE PROBLEMS OF PREGNANT ADOLESCENTS

The stresses of growth associated with pregnancy may have detrimental effects on the nutritional status of an adolescent girl who enters pregnancy in a marginal nutritional state. The nutritional needs during the growth spurt may leave the adolescent with low or depleted stores. About 840 g new tissue are laid down per month in the adolescent growth spurt. This is comparable to the tissue synthesis rate during the last trimester of pregnancy (2), so the nutritional stress of pregnancy may be as great as the adolescent growth spurt. Hepner noted that the frequency of low biochemical values, suggesting nutrient depletion, increases sharply with and immediately following the adolescent growth spurt (2). Growth of children in borderline nutritional states appears to be affected in two ways; it may continue at the normal rate and precipitate malnutrition or growth may be slowed in order to protect against malnutrition (2). If this is also true for pregnant teenagers with marginal nutrition, the fetal growth needs may cause manifest maternal

malnutrition and/or fetal growth may be slowed to protect the maternal nutritional state. For those girls becoming pregnant during their adolescent growth phase, the problem may be more ciritical. Presently, the mean age at menarche is about 12.5 years (3) and the pubertal growth spurt occurs about 18 months earlier, or at 11 years on the average. Therefore, the average growth rates of adolescent girls are diminishing rapidly by age 12 and are very small after age 14 even though growth in stature does not cease until about age 18 (4). It is, then, the pubertal groups of girls, i.e. on the average those aged 14 or less, in whom combined stresses of growth and pregnancy may be present. The medical course of pregnancy in these girls is often more complicated than the course of those girls over 14.

Protein and energy supplies appear to be critical for normal tissue synthesis during pregnancy and growth. Insufficient amounts of either as well as zinc may compromise growth and development. Lack of iron in the diet can cause maternal anemia and reduced fetal iron stores. Therefore, the pregnancy requirements for thse nutrients will be discussed in detail.

BASIS OF PREGNANCY NUTRIENT RECOMMENDATIONS

Protein

Protein requirements during pregnancy have been determined on a largely theoretical basis. Additional protein and, therefore, nitrogen (N) is thought to be needed solely for the synthesis of fetal tissue and maternal tissues associated with pregnancy. The amount of protein deposited in the tissues of pregnancy at term is 925 g, or 148 g N, on the average in healthy, Anglo women gaining approximately 12.5 kg (27.5 lb) (Table 2). Associated with the protein in these tissues is 320 mEq potassium (K), so the K:N ratio of the pregnancy tissue is 2.16 mEq K per g N. It is believed that tissue is not accumulated at a steady rate during pregnancy, but rather that there is little protein deposition early in pregnancy, 0.64 g per day in the first quarter, which increases 10 fold to 6.1 g per day during the last 10 weeks of pregnancy (5).

The theoretical protein recommendation has no provisions for a maternal gain of lean tissue associated with pregnancy. Over 250 N balance (N intake minus N output from all body sources) studies of women in the latter half of pregnancy imply that some maternal lean tissue may be retained. Anthropometric measurements confirm this observation (6). The women participating in the balance studies retained 1.1g N/day on the average, about 0.3 g N/day more than that accounted for by the components of pregnancy (7). A maternal gain of 0.3 g N per day would result in accumulation of 9.6 g lean tissue daily (N X 32, Reifenstein factor (8)), or about 1.3 kg throughout the latter half of pregnancy if the rate of maternal lean tissue storage is constant during this time.

Data from pregnant teenagers suggest that they also gain maternal lean tissue. Nitrogen storage was measured by the balance technique in a group of pregnant adolescents during the latter half of pregnancy (9). The 10 primiparous adolescents in this study were all considered to be healthy, but many came from low income clinic populations and had histories of poor diet intakes. N intake ranged from 9.3 to 20.0 g per day or from 10.5 g (the 1968 RDA) to 19.5 g/day for a girl of reference body size. Energy intake ranged from 35 to 53 kcal per kg but was fairly constant for most subjects at all levels of N intake.

Nitrogen retention varied directly with N intake ($r = 0.680$, $p \leq 0.01$) over the entire range studied, and the relationship was described by the following equation: N balance, g/day = -1.73 + 0.30 (N intake, g/day). When the lowest level (equivalent to the 1968 NRC-RDA) was fed 1.4 ± 0.5 g N was retained on the average. As much as 4 to 6 g N was stored when the diet supplied about 18 g N. The average N retention over all diet levels and periods in these 10 pregnant teenagers was 2.42 ± 1.18 g N per day; this amount is about three times the theoretical storage (0.8 g N/day) accounted for by the components of pregnancy. It appears that pregnant adolescents, like pregnant adults, store more N than accounted for by the theoretical pregnancy components.

For those who remain unconvinced by the data due to the questioned validity of the N balance technique, additional evidence of maternal lean tissue storage offered by whole body ^{40}K counts and total weight gain in this study (9). The observed weight gain of the pregnant adolescents during the study was 77 ± 25 g per day. If their N retention averaged 2.42 g/day, the associated gain in lean tissue would be 77 ± 37 g/day (N x 32), so a hypothesis of true N storage is possible.

Total body potassium content was measured by whole body ^{40}K counts at the beginning and end of the study period in 8 of the 10 girls. The whole body ^{40}K data indicate that potassium accretion averaged 3.41 ± 0.94 mEq per day. The components of pregnancy account for 320 mEq K accretion at term, and it is assumed to be deposited in a K:N ratio of 2.16 mEq K/g N (Table 2). Therefore, a daily accumulation of 800 mg N/day during the last half of pregnancy would be associated with 1.74 mEq K accretion. The measured K deposition, 3.41 mEq, was nearly double this amount. If maternal tissue gain is based on the ^{40}K data, 3.6 kg of lean wet tissue would have been gained during the latter half of pregnancy. (Continued on next page.)

ENERGY

Additional energy is required during pregnancy for building new tissue, for increased work load associated with the movement of a heavier body, and for an increase in the resting metabolic rate. New tissue synthesized daily during the last half of pregnancy has an energy equivalent of approximately 150 kcal (628 kJ). This energy equivalent is based on the assumption that the maternal tissue gain is solely fat tissue, and since the energy value of fat tissue is about 9 kcal/g whereas lean tissue is approximately 5.6 kcal per g, this energy equivalent would be overestimated if one-half to three-fourths of the maternal gain is lean tissue.

The energy cost of activities was studied in a group of teenage primigravidae (10) who were also participants in the study of dietary protein needs (9). Resting, fasting metabolic rates (RMR) measured in eight of the subjects 4 to 17 weeks after parturition were compared with basal metabolic rates (BMR) measured the last trimester. The mean RMR, 0.95 ± 0.16 kcal per minute, was less than the BMR of this sub-group of girls during pregnancy, 1.11 ± 0.14 kcal/minute. Pregnancy rates were 17 percent higher than postpartum values for the group, and individual differences ranged from 3 to 36 percent. Therefore, the net increase in energy required for basal metabolism is equivalent to an additional 230 kcal (964 kJ) per day.

Based on this evidence of maternal lean tissue gain and lowered efficiency of protein utilization in pregnancy, the 1974 NRC-RDA (1) suggest 30 g additional protein for pregnant women of all ages, or 1.3 g protein per kg pregnant bodyweight. The computed allowance for a teenager weighing about 60 kg, or 130 lb., at conception would be about 85 g protein per day during the latter half of pregnancy. This level of protein should allow for maximal protein deposition.

The energy cost of a variety of grooming, household and work tasks was measured in the same subjects in pregnancy and postpartum (Table 3). For sitting activities, energy expenditure was in the order of 1.5 kcal/minute during pregnancy and 1.3 kcal/minute postpartum. This difference is about the same magnitude as between the BMR and RMR values. Household tasks required 17 percent more energy during pregnancy than postpartum, but when differences in body weight are taken into account, the increase is negligible. Postpartum girls expended 3.74 kcal per minute climbing stairs whereas pregnant girls expended only 3.25 kcal/minute, but the pregnant subjects spent 0.80 ± 0.12 minutes completing a 9.2 m ascent and the same girls completed the ascent in 0.65 ± 0.03 minutes postpartum. The cost of the total task was actually higher in pregnancy (2.6 vs. 2.4 kcal for the climb).

In summary, there did not appear to be any difference in energy expended, per unit of body weight for low work level tasks. But, when the work level was heavier and involved whole body movement, work pace slowed and energy expenditure per unit time was less during pregnancy than postpartum, but the energy cost of the complete task was greater for the pregnant woman. The cost of performing programed work on the bicycle or treadmill was the same per unit of body weight in pregnancy or postpartum so pace appears to be a dominant variable.

The implications of these energy studies are as follows: If the pregnant woman is employed doing externally paced work involving body movement, e.g. assembly-line work, her energy expenditure will increase according to her increase in body weight. If left to her own inclination, a pregnant woman may slow her pace so that she works at a slower more comfortable rate for a longer period, if necessary.

In order to evaluate the energy expenditure of free-living pregnant adolescents, diary records of daily activities were kept by a second group of adolescents (10). The energy cost of activities measured in the first group was used to estimate the daily energy needs of the second group. The adolescents were very sedentary, spending about 90 percent of their time lying down or seated. The energy cost of their basal metabolism and activities was computed to be about 2200 to 2300 kcal per day. Therefore, the total metabolizable energy need for these very sedentary teenagers was about 2400 kcal per day (2200-2300 kcal per day for the BMR and work plus 150 kcal per day for energy value of tissue synthesis). A more active adolescent would require more energy in her diet. The 1974 NRC-RDA (1) for energy is 300 additional kcal (1255 kJ) per day for all pregnant women and not less than 36 kcal per kg pregnant body weight. This recommendation may not be adequate for pregnant women doing active activity several hours each day.

ZINC

The Food and Nutrition Board recommended 5 additional mg zinc for pregnancy in 1974. The basis of this recommendation is not stated in the text, but it was computed by assuming that the average weight gain of healthy pregnant women, 12.5 kg, could be all lean tissue containing 30 ppm zinc (11). The total accretion in pregnancy computed thus would be 375 mg zinc, or 1.4 mg per day. If about 25 to 30 percent of dietary zinc is absorbed, then 5 mg would have to be added to the diet. The RDA for pregnant adolescents and adults is 20 mg zinc per day.

IRON

The iron needs for pregnancy are equal to the amount of iron lost by the mother at delivery, i.e. the iron in the fetus, the placenta, and the blood loss. About 370 mg iron are deposited in the products of conception, and an additional 250 mg iron are lost at delivery if about 600 ml blood are lost with a hematocrit value of 37 (12). These sources of iron loss total 660 mg. Most of the fetal, placental and blood iron is gained in the last half of pregnancy. Therefore, over the last 140 days 4.7 mg iron must be gained daily. Iron stores and/or dietary iron are the available sources of this iron. As the iron stores in healthy American women only average about 0.3 g (13), and they may be even lower in adolescents, additional dietary iron is needed. Normally, only about 10 percent of dietary iron is absorbed, but the efficiency or iron absorption increases progressively during pregnancy reaching a peak of 25 percent in the last trimester (14). Thus, the total pregnancy iron needs could be obtained from diets containing 18 mg iron. Most pregnant women consume less than 18 mg iron per day, usually about 13-14 mg. Since many women often have very low iron stores, a supplement of 30 to 60 mg elemental iron, such as ferrous sulfate, ferrous fumarate, or ferrous gluconate, is often recommended.

DAILY FOOD GUIDE FOR PREGNANCY

Recently a Daily Food Guide has been developed to meet the 1974 NRC RDA's for pregnancy (Table 4) (15). The food guide is a modification of the Basic Four Food Guide designed by the U.S. Department of Agriculture in 1953. The dairy, meat, grain and fruit and vegetable groups are retained, but subdivisions are made within each group to improve the nutrient intake of lesser known vitamins and minerals. As with any food guide, there is a certain amount of day to day variation in the actual nutrient intake depending upon which food items are selected, but the guide assures an average intake of essential nutrients which is acceptable. However, it is extremely difficult to meet the Recommended Dietary Allowances for folacin and vitamin B_6 during pregnancy. Re-examination of the recommendations for these nutrients is necessary as one must rely on supplements in order to meet the current recommendations. Clinical studies do not always confirm the need for supplemental folacin and vitamin B_6 in pregnancy.

The RDA for energy is not meant to be achieved by this food guide. In order to consume adequate calories, the woman should be counseled to include additional foods in her daily diet. The Daily Food Guide contains more protein than recommended by the RDA; about 100 to 120 g protein are provided in diets based on the Guide. The RDA level of protein must be exceeded in order to have adequate intakes of other nutrients. Protein foods contribute significant amounts of vitamin B_6, iron and zinc.

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Table 1. Recommended Dietary Allowances[a] for Pregnant Adolescents and Adults

	Increment recommended for pregnancy	Adolescent recommendation	Adult recommendation
Energy, kcal	300	2400 (or 36 kcal or more per kg gravid weight)	2300 (or ≥ 36 kcal/kg gravid weight)
Protein, g	30	78 (or 1.3 g/kg gravid weight)	76 (or 1.3 g/kg gravid weight)
Vitamin A, IU	1000 (200 RE)[b]	5000 (1000 RE)	5000 (1000 RE)
Vitamin D, IU	-	400	400
Vitamin E, IU	3	15	15
Ascorbic Acid, mg	15	60	60
Folacin, µg	400	800	800
Niacin, mg	2	16	15
Riboflavin, mg	0.3	1.7	1.5
Thiamin, mg	0.3	1.4	1.3
Vitamin B_6, mg	0.5	2.5	2.5
Vitamin B_{12}, µg	1.0	4.0	4.0
Calcium, mg	400	1600	1200
Phosphorus, mg	400	1600	1200
Iodine, µg	25	140	125
Iron, mg	Suppl.[c]	18 + Suppl.	18 + Suppl.
Magnesium, mg	150	450	450
Zinc, mg	5	20	20

a/ See reference 1.

b/ Retinol equivalents.

c/ Supplemental iron is recommended.

Table 2

Components Added in Normal Pregnancy at 40 Weeks

	Weight g	Protein g	Fat g	K mEq
Fetus	3400	440	440	154
Placenta	650	100	4	42
Amniotic Fluid	800	3	0.5	3
Uterus	970	166	3.9	50
Mammary Gland	405	81	12.2	35
Blood	1250	135	19.6	28
Extravascular ECF	1680			8
TOTAL	9155	925	480	320
Observed Gain	12500			
Difference	3345 (Counted as fat)			

From: Hytten, F. E. and I. Leitch. The Physiology of Human Pregnancy. 2nd edition. Oxford, England: Blackwell Scientific Publications. 1971.

Table 3. Energy Cost of Work During Pregnancy and Postpartum in the Same Subjects[a/]

Activity	Paired Subjects			
	Pregnant		Postpartum	
	kcal/min	cal/kg/min	kcal/min	cal/kg/min
Basal	1.11 ± .14 (7)[b/]	16 ± 2	.95± .16	16 ± 2
Sitting	1.32 ± .14 (5)	22 ± 3	1.02± .03	19 ± 2
Sitting (combing hair)	1.36 ± .14 (5)	24 ± 5	1.22± .08	22 ± 2
Sitting (knitting)	1.55 ± .12 (3)	20 ± 1	1.47± .16	20 ± 3
Standing	1.41 ± .19 (5)	23 ± 4	1.12± .14	20 ± 1
Standing (washing dishes)	1.63 ± .08 (3)	28 ± 3	1.33± .34	25 ± 4
Standing (cooking)	1.66 ± .09 (3)	28 ± 2	1.41± .32	26 ± 3
Sweeping (with broom)	2.90 ± .84 (3)	44 ± 11	2.50± .72	43 ± 8
Bed Making	2.98 ± .60 (4)	48 ± 8	2.66± .26	47 ± 6
Ascending Stairs (own pace)	3.25 ± .46 (4)	52 ± 4	3.74±1.08	66 ± 12
Ascending and Descending Stairs	2.55 ± .91 (3)	44 ± 14	3.19± .32	60 ± 6
Bicycle 300 kpm	4.12 ± .55 (7)	67 ± 15	4.27± .44	67 ± 11
Treadmill (3 mph, 0 grade)	4.00 ± .99 (6)	57 ± 7	3.96± .71	63 ± 5

a/ Adapted from Blackburn and Calloway, ref. 10.

b/ Number of subjects included in the mean ± SD.

Table 4. Daily Food Guide for Nonpregnant, Pregnant and Lactating Women.

Food Group	Number of Servings[a/]		
	Nonpregnant	Pregnant	Lactating
Dairy Foods	2	4	5
Protein Foods			
Animal Sources	2	2	2
Vegetable Sources	2	2	2
Whole Grain Cereal Products	4	4	4
Fruits and Vegetables			
Leafy Green Vegetables	1	1	1
Citrus Fruits and Vegetables	1	1	1
Other Fruits and Vegetables	2	2	2
Fats and Oils	2 tbsp.	2 tbsp.	2 tbsp.

a / Serving sizes: Dairy Group:

1 cup
Cheddar Cheeses, 1 oz (except blue cheese, 2 oz.)
Cottage cheese, 1 cup
Ice cream, 1 cup
Pudding, 1/2 cup
Cream soup, 1 cup
Yogurt, 1 cup

Animal Protein:

Beef, pork, lamb, poultry, fish - 1 oz.
Eggs - 1
Frankfurters - 1

Vegetable Protein:

Legumes: 3/4 cup cooked
Nuts: 1 oz.

Whole Grain Products: 1 slice bread
1 oz. dry cereal
3/4 c cooked cereal

(Continued on next page.)

Table 4. Continued

a/ Serving sizes:

Leafy Green Vegetables:	3/4 c. cooked; 1 c. raw
(broccoli, cabbage, collards, lettuce, mustard greens, spinach)	
Citrus fruits and vegetables:	3/4 c. cooked 1/2 c. juice
Other fruits and vegetables:	3/4 c. cooked; 1 c. raw

Nutrition and Mental Development

MYRON WINICK, M.D.*

In a world where population is increasing at an enormous rate, we find one half of that population not adequately nourished.[27] Moreover, this is the half which is multiplying most rapidly. In spite of the efforts in the past few years to deal with this dilemma, the situation is becoming worse. Each day several hundred thousand children are born, most of whom will be exposed to severe undernutrition during their most formative years. Some of these children will die. In some areas only half will survive. Malnutrition will be a major contributing cause of death in most of these children. Infectious diseases which are innocuous in well-nourished populations may be fatal in the undernourished child. Measles, for example, carries an extremely high mortality rate in developing countries. If this were the only dimension, the problem would be serious enough, but at least the survivors could be helped. During the past 20 years, however, evidence has been mounting that an infant who has survived a period of severe malnutrition may be seriously handicapped – handicapped in terms of his physical and mental development. The implications of such evidence are staggering. The vicious cycle which is set in motion is self-perpetuating and continues from generation to generation.[13] The malnourished infant growing up in poverty is unable to acquire the skills to deal with the complexities of modern society. The result is that he remains poor for the rest of his life and his children are born into the same social and economic conditions. The family does not have the resources to adequately nourish the new infant. He in turn becomes seriously malnourished and, if able to survive, is handicapped in such a way as to prevent him from extricating himself from the plight of his parents. Thus a condition of poverty is perpetuated and will be passed from one generation to the next. The genetic endowment is presumably normal, but the environment prevents achievement of the genetic potential. This analysis suggests that there already exists a pool of people who have been so handicapped, and that this pool is increasing in almost geometric proportions with the present-day population explosion.

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In this paper I should like to examine critically the evidence that has led to these serious conclusions, and to examine some practical possibilities for interrupting this cycle.

Studies from a variety of sources indicate that in both animal and human children a series of critical periods exists, as the brain develops, during which environmental stimuli may produce irreversible damage. We can arbitrarily divide these studies into those dealing with the physicochemical development of the brain and those dealing with the functional development of the brain. Studies in each of these areas can be further divided into those performed in animals and those carried out in humans.

PHYSICOCHEMICAL GROWTH OF THE BRAIN

Animal Experiments

Eighty percent of adult brain weight is reached by 1 month of age in the rat and by 2 to 2½ months of age in the pig. In all species of mammals so far studied, the brain reaches its ultimate weight long before the animal reaches its mature size. The brain almost invariably is the first organ to attain its final size. It was first demonstrated 50 years ago that undernutrition in rats shortly after weaning resulted in reduced brain weight, and that this reduction persisted even after the animal was nutritionally rehabilitated.[28] These results have not only been confirmed in both rats and pigs,[16, 17] but have been extended[41, 43] to show that even more marked and long-lasting effects could be obtained if the animals were undernourished from birth to weaning.[42] At present there is little doubt that malnutrition from birth to 21 days of life will result in a permanent reduction in brain weight. More recent studies in the rat have indicated that brain weight may be reduced even in utero by severe protein restriction in the mother, and that animals born to such mothers may never achieve normal brain size even if they are adequately nourished after birth.[44] In contrast, undernutrition after 3 weeks of age in the rat and after 5 weeks of age in the pig results in progressively smaller effects on brain weight and complete recovery of normal weight after rehabilitation. These studies have repeatedly demonstrated that the time in which malnutrition is occurring is critical in terms of the ultimate outcome. The earlier the malnutrition, the more severe is the effect and the less likely is recovery. It would appear that a critical period of brain growth exists in the rat and in the pig, during which the brain is most susceptible to the effects of malnutrition.

HISTOLOGIC CHANGES. Histologic changes have been observed in the central nervous systems of rats, pigs, and dogs raised from weaning on protein-deficient diets.[15, 16] Both neurons and glia in spinal cord and medulla degenerate. These changes persist even after intensive rehabilitation with a protein-rich diet lasting for as long as 3 months. The changes could be made more severe either by beginning the restriction at an earlier age or by extending the duration of the deficient diet. In pigs

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Personal communication.

it has also been demonstrated that severe undernutrition early in life will produce histologic changes in the cortex itself.[30] Neurons in gray matter are reduced in number and appear swollen. More recently, histochemical changes have been described in the brains of rats subjected to early malnutrition. The appearance of a variety of enzymes, demonstrable by special staining techniques is delayed and the ultimate quantity obtained is reduced.[55] Thus early malnutrition will produce specific histologic and histochemical changes within the cells of the central nervous system. Again, the earlier the malnutrition, the more severe is the damage and the more likely it is to persist.

CELLULAR GROWTH. Weight gain and histologic appearance give only a limited picture of organ growth. Organ growth may be quantitated in terms of increases in cell number and increases in the weight or protein content per cell. Since DNA is constant within any diploid cell in a given species,[3] the amount of DNA in any organ reflects the number of cells in that organ at any given time. The actual number of cells may be calculated by determining total organ DNA and dividing by the DNA content per cell.[22] Once the number of cells is known, the average weight per cell or protein per cell may be determined simply by dividing the total organ weight or protein by the number of cells.

Normal and retarded growth in the organs of the rat have been serially studied in this manner.[49] Three phases of growth were defined in all organs: hyperplasia, hyperplasia and hypertrophy, and hypertrophy alone. The transition from one phase into another depended on a slowing down and finally a cessation of DNA synthesis. The time this occurred varied from organ to organ, but in all cases DNA synthesis, as measured by total organ analysis and by incorporation of ^{14}C-thymidine, ceased before weight gain and net protein synthesis stopped.

In the whole brain, DNA synthesis stopped at 17 days, whereas net protein continued to increase until 99 days. Moreover, if the brain is divided into specific regions, these areas have their own individual growth patterns.[23] Cell division in the cerebellum proceeds at a rapid rate until 17 days and then abruptly stops. In contrast, the increase in cell number in the cerebral cortex proceeds more slowly but lasts until 21 days. In the brain stem there is an increase until 14 days and then a leveling off, whereas the hippocampus has a discrete increase between 14 and 17 days. This discrete rise in DNA content is probably associated with migration of cells into the hippocampus rather than with cell division within the hippocampus itself. Total protein content increases at a more rapid rate than total DNA in the cerebrum and brain stem. In the cerebellum, however, protein increases more slowly than DNA. Therefore, protein/DNA ratios rise in the brain stem and cerebrum but actually decrease with growth of the cerebellum.

Because previously cited experiments suggested that the recovery patterns of early and late malnutrition differed, the effects of malnutrition on these cellular growth patterns were investigated.[47]

Results indicated that early restriction interfered with cell division and that the animal was left with a deficit in the number of cells in all organs, even after adequate refeeding. Late malnutrition resulted in a decrease in the protein/DNA ratio (cell size), with recovery on refeeding.

In those animals malnourished from 21 to 42 days, all organs were reduced in weight and protein, but the brain and lung had normal DNA content, while the others had reduced DNA content. Thus, in the brain and lung, "cell size" was reduced with no effect on cell number, whereas in the other organs, cell number was reduced, "cell size" remaining normal. Only the brain and lung recovered on refeeding.

These data supported the hypothesis that interference with cell division resulted in "permanent" effects and focused attention on the first 21 days of life, at least as far as the brain was concerned. Moreover, since only the whole brain had been examined, the various regions of the brain in animals exposed to neonatal malnutrition were studied.

In rats malnourished from birth the cerebellum showed a reduced DNA content by 6 days of age, whereas changes did not appear in the cerebral cortex until 14 days. Migration into hippocampus, which usually occurs between 14 and 17 days, was delayed.[24] Thus, at least in the brain, different regions show selective sensitivity to malnutrition which appears to depend on the cellular events occurring in that region at that time. Recent studies employing radioautography have elucidated the cell types involved. Results indicate that it is not the cell type, but whether it is dividing, that is critical. Thus, postnatal undernutrition will affect only glia in rat cortex since only glia are dividing. However, in cerebellum and under the ventricles where neuronal elements are dividing, these cells are affected and their rate of cell division is curtailed.

Conversely, "overnutrition," produced by reducing the litter size to three animals nursing from a single mother, resulted in an increased brain weight which was associated with an increase in the number of cells.[48] Thus, the rate of cell division and the final number of cells could be altered in either direction by the state of nutrition. It therefore seemed possible that recovery actually might occur even if cell division had been interfered with, if the animals were refed increased quantities and if refeeding were begun before the normal period of cell division had stopped.

Animals were reared in groups of 18 until 9 days of age and then reared in groups of three until weaning. The reduction in cell number which was present at 9 days in all organs disappeared by weaning. In the brain, only the cerebellum showed a significant reduction in DNA content at 9 days, and by 21 days this reduction had disappeared.[52] These data demonstrated that during the period of hyperplasia, the rate of cell division may be increased sufficiently, by increasing caloric intake, to correct a previous deficit in cell number imposed by malnutrition. Thus, not only are the extent and duration of undernutrition and rehabilitation important, but the age of the animal at the time rehabilitation begins is also critical. It is important to note that this recovery is for total brain cell number and says nothing about individual brain regions and specific cell types.

Recent evidence of Zamenhof and associates[54] demonstrates that malnutrition during pregnancy in rats will result in offspring whose brains contain a reduced number of cells. Data from our laboratory[46] have indicated not only that this is true, but that as early as 16 days of fetal life, cell division is retarded in all areas studied and every cell

type is involved. Moreover, even if the young feed normally after birth, they do not recover and are left with a permanent deficit in brain cell number. However, it is perhaps even more significant that the effects of postnatal malnutrition on animals previously malnourished in utero are much more marked than the effects of either type of malnutrition alone. These "doubly deprived" animals are severely retarded in their growth, and their brains contain only 40 per cent of the expected number of cells. It is as though prenatal malnutrition has conditioned these animals and made them hypersensitive to postnatal undernutrition.

All these studies demonstrate that a critical period of brain growth can be defined in terms of cell division. Cell division stops in the brain long before growth per se is over. Moreover, different regions reach their final number of cells at different times. Malnutrition curtails cell division during this critical period and can permanently reduce the ultimate number of cells. In the rat this critical period of cellular proliferation lasts only until weaning (21 days of age).

MYELINATION. Myelin is a complex lipid made up of a number of components. About 70 percent of total rat brain cholesterol is present in myelin. Nearly all of the cerebroside and most of the phosphatidal ethanolamine (plasminogen) in the rat brain appear to be located in myelin, and about 70 percent of total brain sulfatides and sphingomyelin is also present in this complex lipid.[14] Thus, analysis for these substances will give a quantitative estimation of the amount of myelin present in the brain. Moreover, since there is very little myelin turnover within the brain, serial estimation of these components can be used to establish the rate of myelin formation. The rate of myelin formation can also be established in experimental animals by measuring the rate of incorporation of radioactive components into the myelin structure.

Myelination occurs at different times in various areas of the nervous system, and its time of onset varies in different species. The process is preceded by a proliferation of oligodendrocytes.[2] Thus, myelination is dependent at least in part on cellular growth of various brain areas, and may be influenced indirectly by factors affecting the cellular growth pattern of brain as described in the previous section.

The apparent metabolic stability of myelin constituents, once laid down, makes possible the use of analytic procedures to measure brain growth. Although certain stimuli may retard the rate of myelin formation, it is unlikely that these stimuli can actually reduce the amount of metabolically stable material already there. In this respect, myelin resembles DNA. Hence, as with ultimate cell number, total myelin content should be severely reduced only if undernutrition is imposed during that period when myelin is most rapidly being laid down. In the rat, the most rapid phase of myelination is from 10 to 21 days. The incorporation of sulfate and galactose into cerebrosides and the entry of preformed cholesterol and of cholesterol precursors into brain in vivo are maximal during this period. The same is true of in vitro incorporation of phosphatide precursors into myelin phospholipids.[14] Again, a critical period can be described, this time in terms of most rapid rate of myelination, and again, this period occurs before weaning in the rat. Malnutrition during this critical 3 week period produces substantial deficits in total

brain cholesterol and a lowering of cholesterol concentration.[17] In pigs malnourished during the first year of life, total brain cholesterol and phospholipid content are markedly reduced and cholesterol concentration is slightly reduced.[15] These changes, both in rats and in pigs, persist even when the animals are rehabilitated for a long time.

Chase and associates[8] have recently demonstrated that incorporation of sulfatide into myelin of rat brain is markedly reduced both in vivo and in vitro by malnutrition during the first 3 weeks of life. Moreover, the activity of one of the enzymes involved in this incorporation is reduced by this form of neonatal malnutrition. Again recovery did not occur with rehabilitation of the animals.

The bulk of evidence seems to establish that myelination within the rat brain occurs most rapidly during a discrete period. This period is quite similar in time to the period of cellular proliferation described in the previous section. Malnutrition at this time reduces the rate at which myelin is laid down and the ultimate myelin content of the brain. Whether this is a direct effect on the metabolic events within the cells responsible for myelin synthesis or simply a reduction in the number of myelin-synthesizing cells is unknown. The enzymatic data of Chase and associates[8] would suggest that, at least in part, the former is true. Studies of the effect of malnutrition during this critical period on regional myelination patterns indicate that inhibition of myelin synthesis occurs in cerebrum, cerebellum, and brain stem, and that this reduction is proportional to the reduction in cell number described in the previous section.

OTHER. Other chemical parameters of brain growth and maturation have not been extensively studied during experimental neonatal malnutrition. However, some evidence does exist that several other processes may be disturbed. Sereni and associates[38] demonstrated that norepinephrine and serotonin levels in the rat brain are reduced after 8 days of poor nutrition beginning at birth. However, the concentration of these amines returns to normal even if the malnutrition is continued. Studies have shown an increase in the RNA/DNA ratio in the brain after a short period of malnutrition beginning at birth. This change also disappears if the undernutrition is continued.[32] Thus, transient chemical changes, which disappear later, occur during early nutritional deprivation. The significance of these changes is still not clear. Experiments in other organs demonstrate that malnutrition will reduce the rate of protein synthesis and result in disaggregation of polysome patterns.

Current evidence also suggests that the pathways of glucose metabolism in the rat brain may change as a consequence of early malnutrition. The per cent of glucose metabolized through the hexosmonophosphate shunt increases until about 8 days of age, levels off, and then drops after weaning. Malnutrition may alter this sequence. Experiments now in progress indicate that there is a change in the activity of the enzyme DNA polymerase which is in direct relation to the rate of cell division.[1] Activity of this enzyme may provide an ad hoc index of the rate of cell division. The effects of malnutrition on the activity of this enzyme are currently being investigated.

All these studies demonstrate that the preweaning period in the rat is a time of enormous chemical change within the brain, and a time when the brain is most sensitive to the detrimental effects of undernutrition.

Human Studies

The physical and chemical changes that occur during maturation of the brain have been studied less in the human than in other species. Brain weight increases rapidly prenatally and for the first 2 years of life, and more slowly thereafter, reaching adult weight by adolescence.[11] During fetal life the brain not only increases linearly in weight but undergoes a series of biochemical changes.[21] Glycolysis is present during the second month of fetal life, oxidative mechanisms appear during the third month, and activity and localization of a number of enzymes have reached a mature pattern during the seventh month of fetal life. In addition there is evidence that the presence of acetylcholinestrase indicates tissue excitability.[32] The activity of this enzyme is localized in neurons of the anterior horn of the spinal cord as early as the tenth week of embryonic life.[18] This correlates well with the time that movement of the lower limb can be elicited by proper stimulation.[1] Two specific cell types, the Cajal-Retzius cells[20] and the monamine oxidase cells,[19] are present only in fetal life, disappearing before birth. Their function is unknown. Definite lamination of the cerebral cortex is first seen around the twenty-seventh week. These data suggest that a number of critical periods may occur during development of fetal human brain. The effects of adverse stimuli on this development have not yet been studied. Investigations of brains from thirty-one normal children, who died of accidents, poisonings, or crib deaths, and from fetuses removed at therapeutic abortions, indicate that the number of cells within the brain increases linearly until birth and then more slowly until about 8 months of age, after which there is little if any increase in brain cell number.[45] Histologic studies of the cerebral cortex suggest that most neuronal division has ended by the time of birth. However, whether neurons in other areas divide postnatally is unknown. The most rapid period of myelin synthesis in the human brain appears to be around birth, but significant synthesis is still occurring at 2 years of age.[21]

Brown[5] has shown that malnutrition during early childhood will reduce brain weight. There was a marked decrease in the total number of cells within the brain in ten children who died of infantile marasmus during the first year of life in Santiago, Chile.[50] Data from this study indicate that very little cell division took place from the time these children were exposed to severe malnutrition. In four of the cases the DNA content was about 40 per cent of normal. These four children all weighed less than 2000 grams at birth. Unfortunately, their gestational age was not known. These data, however, suggest either that low birth weight infants are more susceptible to neonatal malnutrition or that significant malnutrition has occurred in utero. Studies of lipid content in human brain after severe early malnutrition confirm previous findings in animals. Total lipid content as well as total phospholipids and cholesterol are

reduced. During the first 8 months of life the reduction in lipid is proportional to the reduction in DNA and hence the lipid/DNA ratio or lipid per cell is normal. However, if the malnutrition persists beyond 8 months of age, then the lipid/DNA ratio falls, indicating less lipid per cell.[37]

Regional studies indicate that postnatal cell division is more rapid in cerebrum than in cerebellum, and stops at about 8 to 12 months in both areas. In brain stem, cell division occurs at a slow rate throughout the first year of life. Early malnutrition will reduce the rate of cell division in all three of these areas, producing the most marked reduction in cerebral cell number.[53]

One type of indirect measurement of brain growth is unique to human studies: serial measurement of head circumference. Several groups of investigators in different areas of the world have shown that malnutrition, especially during the first year of life, will curtail the normal rate of increase in head circumference.[40] Furthermore, recent studies suggest that during the first months of life, reduced head circumference in malnourished children accurately reflects the reduced number of cells and reduced lipid content present in their brains.[51]

Hence, available evidence from human studies reinforces the data derived from animal experiments and suggests that there is a critical period of brain growth during early infancy when the brain is extremely vulnerable to the effects of malnutrition.

The effects of malnutrition on the physical and chemical growth of the brain are summarized in Table 1. Both in animals and in humans, brain growth may be retarded by malnutrition. The earlier the nutritional deprivation, the more severe the retardation. There appears to be a critical period during which cell division is rapidly occurring and myelination is proceeding at its more rapid rate. Proper nutrition is essential for these processes to proceed normally. Interruption of cell division or myelin deposition or both during this period will result in permanent

Table 1. *Physical and Chemical Changes in the Developing Brains of Malnourished Subjects*

PHYSICAL OR CHEMICAL MEASUREMENT	ANIMALS	HUMANS
Weight	Decreased	Decreased
Histology	Degeneration of neurons and glia	-
Histochemistry	Delayed enzyme appearance	-
Cell number	Decreased in total brain. Earliest effect on cerebellum	Decreased in total brain, cerebrum, cerebellum, and brain stem
Net protein synthesis	Decreased	Decreased
Cell migration	Delayed in hippocampus	-
Myelin synthesis	Decreased	Decreased
Norepinephrine and serotonin concentration	Transiently decreased	-
RNA content per cell	Transiently increased	-
Glucose metabolism	Altered	-
Head circumference	-	Decreased

deficits within the brain. If animal and human data are examined together, there is a suggestion that prenatal malnutrition may make the brain more vulnerable to a subsequent postnatal insult.

A number of questions remain unsolved. What is the functional significance of these physical and chemical changes? What is the mechanism by which they occur? Although these data construct a picture which clearly demonstrates that nutritional deprivation affects brain growth and structure, and although it is quite tempting to relate these effects to brain function, no causal relationship has been demonstrated. The physical and chemical studies at best provide only strong circumstantial evidence that functional brain damage may result from early malnutrition.

STUDIES OF BRAIN FUNCTION

Animal Experiments

When Platt and associates placed weanling rats and pigs[36] and dogs[35] born of well-nourished mothers on deficient diets, the animals showed functional signs of central nervous system damage. After only 4 days on the restricted diets, the rats developed spasmodic trembling of the head and forepaws. The pigs began to walk on tiptoe with a "hobble skirt" gait and some incoordination of the hind legs. The puppies became hyperirritable. Electroencephalographic changes could be demonstrated in all the animals. Data presented more recently demonstrate actual convulsions and periods of loss of consciousness secondary to undernutrition in puppies.[39] The clinical condition of these animals improves after a short period of rehabilitation. Thus, clinically discernible neurologic damage can be demonstrated in animals undernourished early in life. Although these changes are reversible, more subtle changes conceivably could remain.

Barnes and co-workers have confirmed these observations and in addition have observed decreased learning ability in pigs malnourished early in life, which has persisted even after long-term rehabilitation. These animals do not respond well in certain types of conditioning experiments and have difficulty in solving maze problems. Barnes and Frankova have recently shown that rats malnourished during the preweaning period demonstrate a decrease in exploratory behavior. Novakova and associates[34] demonstrated in rats that early weaning followed by inadequate diet caused a decreased behavioral response to an electric bell sound. Pigs exposed to a relatively short period of undernutrition early in life show persistent functional deficits even if they are "totally" rehabilitated. There is a mild deficit in their ability to be conditioned to a shock stimulus and a marked deficit in their ability to extinguish the conditioned response once it has been learned. Rats whose mothers were malnourished during pregnancy will show decreased exploratory behavior by 10 days of age even if adequately nourished after birth.[9] Recently, Frankova has reported that rats supernourished for the first 21 days of life also showed subsequent learning

deficits.[25] Thus both undernutrition and overnutrition in preweaning rats will result in persistent functional alterations of the brain.

All these studies are highly suggestive. Functional changes can be demonstrated, some transient and some permanent. The stimulus inducing these functional changes can be isolated in animals and proved to be altered nutrition. However, the meaning of these functional differences in terms of over-all learning capabilities is difficult to assess in animal experiments. Although inferences may be drawn about the effects of human malnutrition, the evidence is still only circumstantial. There is a need for more work employing specific behavioral testing and correlating behavioral abnormalities with biochemical data in the same animals. To this end, it should be pointed out that the neurologic symptoms described suggest cerebellar involvement, and the cellular changes produced by malnutrition appear earlier and are most marked in the cerebellum. Preliminary experiments demonstrate decreased cell number, restricted to the cerebellum, in animals having decreased exploratory behavior when tested a few days previously.

Human Studies

Neurologic abnormalities, such as apathy and lethargy, are prominent symptoms of severe malnutrition in children. Both specific and nonspecific electroencephalographic changes also may occur. However, all of these changes are variable and usually disappear with rehabilitation. Gross neurologic sequelae are rare. However, subtle neurologic changes have not been systematically looked for. It would seem to me that this should be a fruitful area for future clinical investigations.

The behavior of children who were severely malnourished as infants has been studied both retrospectively[6, 7, 26, 27] and prospectively.[11–13, 29] It is difficult, however, in both these types of studies to isolate malnutrition as the cause of the mental deficiencies found. These children invariably come from poorer backgrounds, lower socioeconomic conditions, and a generally more deprived atmosphere than even the most carefully matched control groups. Both types of studies also suffer from the lack of standardization of intellectual tests. Tests developed in advanced countries may have little meaning in developing countries, especially if large cultural differences exist. In addition, retrospective studies, although able to examine more children, suffer from not being able to be sure of the criteria used to establish the diagnosis of malnutrition. However, even with all these problems, both types of studies provide valuable data, especially if these data are not overinterpreted and especially when they are considered in the light of animal experiments and physical and chemical studies.

In a retrospective analysis, Cabak and Najdanvic[6] demonstrated that Serbian children with a history of marasmus had significantly lower intelligence quotients than Serbian children in general. This study made no real attempt to control other environmental factors but used controls of the same racial or genetic stock. One important aspect of this particular study is that it deals with malnutrition during the first year of life. Precise time distinctions are often not made in other studies inves-

tigating malnutrition in childhood. It is interesting that this study demonstrates one of the largest intelligence quotient deficits of any of the many investigations and that the patients studied were the youngest when nutritionally deprived. The major weakness in this investigation is the lack of an adequate control group. Normal Serbian children have a certain potential not reached by the study population, but the cause of the retardation cannot be ascribed specifically to malnutrition. The control children not only were better nourished but came from much better socioeconomic environments.

Other retrospective studies in developing countries throughout the world in which more careful control groups were chosen suggested again that early malnutrition interfered with subsequent learning ability. More recently Chase[7] has reported that infants in our own country who were severely malnourished early in life performed consistently poorly when subsequently tested at a later age.

A number of prospective studies have been done or are currently being done. Stoch and Smythe,[40] studying South African children, have shown that those malnourished early in life are smaller than a control population and have reduced head circumferences and intelligence quotients even after longterm follow-up. The intelligence quotient testing has been adapted for South African children and would appear valid. However, again, the control population leaves much to be desired. The malnourished children lived in inadequate housing with no sanitary facilities, came from broken, poverty-stricken homes, and were almost entirely neglected. Control families lived in neat brick houses which had sanitary facilities; all the fathers and mothers were employed, and all the children attended nursery school. Again, we see retardation but cannot isolate nutrition as the cause. However, the study dramatically points out the long-term effects produced by this complex of social ills, of which malnutrition is certainly a prominent member.

This problem of control populations is not easily solved by using control groups from "matched socioeconomic backgrounds." Garrow and Pike[26] have attempted to employ as a control group siblings not having a history of hospitalization for malnutrition. Their data indicate that the malnourished group does catch up to the control group. Here we see the opposite problem. Under these conditions, the control children probably were also malnourished, certainly subclinically and perhaps even clinically. Thus the authors may be comparing malnourished children with malnourished control children. It is significant that both groups of these Jamaican children had poorer growth than generally accepted Jamaican norms and significantly retarded growth by United States standards. The problem becomes exceedingly difficult since one must study similar populations in which nutrition is the only variable.

One of the best series of studies to date is that of Cravioto and others[11-13] in Mexico and Guatemala. They have studied populations of uniform socioeconomic backgrounds. In these investigations, performance on psychological tests was found to be related to dietary practice and not to differences in personal hygiene, housing, cash income, crop income, proportion of income spent on food, parental education, or other

social or economic indicators. Moreover, these investigators found that the performance of both pre-school and school children on the Terman-Merrill, Gesell, and Goodenough draw-a-man tests was positively correlated with body weights and heights. These tests had been previously adapted for the Mexican population being studied. Further investigations in collaboration with the Institute of Nutrition of Central America and Panama (INCAP) in Guatemala again showed a positive correlation between size and performance. The tests included placing blocks in openings, tracing block shapes, and differentiating block shapes by feel alone. These tests were considered to be measures of visual, haptic, and kinesthetic sensory integration, respectively. This study has been interpreted to demonstrate perceptual defects in children exposed to severe early malnutrition. Again, great care was taken in these studies to standardize testing procedures and to eliminate variables other than malnutrition. Although not completely successful, these studies are of the general type that should supply more precise data.

It is significant that in these studies the earlier the malnutrition, the more profound the psychological retardation. The most severe retardation occurred in children admitted to the hospital under 6 months of age and did not improve on serial testing even after 220 days of treatment. Children admitted later with the same socioeconomic background and the same severe malnutrition but a different time of onset did recover with prolonged rehabilitation. This recovery of older children, even when severely malnourished, has been observed before. Kugelmass and associates[29] demonstrated retardation in a group of malnourished New York children over 2 years of age. With prolonged rehabilitation these children significantly increased their intelligence quotient scores. Thus, it is possible that time rather than nutritional state may be of paramount importance in determining whether or not sequelae will be permanent. Data from a study[31] still not complete indicate that Chilean children admitted to a special nutrition unit with severe marasmus below 6 months of age remain retarded in physical, motor, and mental development at least until 5 years of age (when the last testing was done). It is interesting that these survivors of marasmus are from the same population and were admitted to the same unit as those who succumbed and showed the marked physicochemical changes described in the last section. Thus, if the child died he showed reduced brain cell number and myelin content. If he survived he was permanently stunted in size and retarded in development. This is the first study, with all its obvious drawbacks, which attempts to correlate changes in brain structure with those of brain function.

A final study should be mentioned,[10] though it is still in progress and therefore cannot be critically evaluated. This is the study currently being conducted at INCAP. Aware of the inherent problems of control populations and of validity of testing, these investigators have set up a study in three villages. Great pains have been taken to assure that these villages have comparable populations. Food is supplied in one village, which is otherwise left alone; both food and social improvement are introduced into the second village; the third village is simply observed

Table 2. *Functional Changes in the Developing Brains of Malnourished Subjects*

FUNCTIONAL CHANGES	ANIMALS	HUMANS
Neurologic symptoms	Transient; tremors, hobble skirt gait, convulsions	Transient; apathy, lethargy, or hyperirritability
EEG changes	Increased slow wave activity (transient)	
Behavioral	Decreased "exploratory" behavior	Exaggerated response to certain stimuli
	Poor ability to extinguish a response	Poor ability to extinguish a response
Intellectual	Difficulty in maze learning	Decrease in cognitive and perceptual development*

*Malnutrition has not been entirely isolated as the sole cause of these changes.

The study has gone on for only a short time, but available data suggest that supplying food alone may significantly alter subsequent mental performance.

Although all these human studies clearly demonstrate retardation in development, they only implicate mainutrition as a cause. Although more work must be done, the data are nevertheless becoming more and more impressive when viewed as a whole. Each study has its own particular flaw, but since the flaws in each study are not the same, many of the variables cancel when the studies are combined. One common denominator seems to remain: severe early malnutrition.

Even if malnutrition is not the sole cause of the retarded development which has been described, the young infant is certainly most at risk. We can certainly conclude that the complex of social ills encompassing severe malnutrition, which is prevalent throughout the world, affects the learning ability of infants. The infant population is not being protected adequately from what would appear to be permanent disability. Table 2 summarizes the functional abnormalities produced by malnutrition both in young animals and in children.

COMMENT

Three questions must be answered in assessing the consequences of nutritional deprivation on ultimate potential. (1) Does malnutrition in itself produce significant brain changes? (2) If so, are these changes functionally important? (3) Is there a time during development when the brain is most susceptible to these changes?

The animal evidence presented seems certainly to establish that malnutrition as an isolated variable will produce physical, chemical, and functional changes in the brain. The data also establish that these changes are most marked and least reversible during the preweaning period in rats and shortly after birth in pigs. The meaning of these changes is difficult to interpret in animals. Certainly function is impaired, but whether these animals are retarded is impossible to say. The

weakest link in the chain of animal experiments is the lack of standardization of the behavioral tests employed and the lack of correlation between structural and chemical changes and behavioral abnormalities.

The human data again demonstrate physical and chemical changes in the brain, and the studies of nucleic acid, protein, and lipid content isolate malnutrition as the offending agent. Both these studies and the behavioral studies point to the first 6 months of life as the critical period. Furthermore, the psychological data clearly demonstrate that functionally significant retardation occurs.

The human data are weakest in answering the first question. Existing conditions within developing countries and within certain segments of our own country make it impossible to isolate malnutrition from other consequences of poverty. Certainly the complex of socioeconomic evils that includes malnutrition tends to produce retarded development. Experiments that have attempted to isolate the nutritional component have only partially succeeded. Some experiments have eliminated certain variables, while others have eliminated some of the other variables. In all, malnutrition was certainly most prominent. More data must be collected, but the evidence is becoming more and more weighty that malnutrition in infancy permanently affects the minds of the children who have been afflicted. The details have still to be worked out. How much undernutrition? What kind? When, if ever, is the brain no longer susceptible? How severe is the retardation? In other words, the degree is still an open question, but certainly severe malnutrition of young infants will produce significant brain damage.

From a practical standpoint, these conclusions are not aimed at pointing out what everyone is already agreed on—that malnutrition is undesirable. Certainly none of these experiments with animals or complicated human studies is necessary to make this point. But these studies do point out two considerations that have important practical consequences. First, as pointed out in the introduction, malnutrition is a self-perpetuating problem, a vicious cycle which begins in infancy and condemns a person to a lifetime of perhaps marginal function, making it that much more difficult for him to extricate himself from the existing conditions and to create for his family an environment which will protect his children from the same "disease." Changes in other organs produced by malnutrition are in certain situations extremely severe. They may kill the patient or keep him in a poor state of physical health, but they do not affect his ability to change his own or his family's life to the same degree as the changes produced in the brain.

Second, the time element is critical; it is perhaps the most important single finding in all these studies. Both the animal and the human data demonstrate very definitely that the earlier the malnutrition, the more severe and the more permanent are the effects. Indeed, the data strongly suggest that permanent effects will not occur if malnutrition begins after a certain age. Although the exact timing has yet to be worked out, it would appear that after infancy the brain is much more resistant to the effects of malnutrition. It is also possible that the infant whose mother was malnourished is more at risk than the infant born to a well-

nourished mother. Therefore, it would seem that the first priority should be the elimination of malnutrition in infancy and perhaps even prenatally.

In many developing countries and even in our own country, infancy has not been the prime nutritional target. A rich country such as this one should not have to establish priorities. However, at the recent White House Conference on Nutrition and Health it was again pointed out that the young infant and the pregnant woman are in an extremely vulnerable group, that a large number of people in this vulnerable group are now living in extreme poverty and are unable to provide themselves or their infants with an adequate diet. In view of the kinds of data reviewed here, certainly a reordering of our priorities would seem in order. In a poorer country strict priorities may be necessary. Although it is important to develop local protein sources, major efforts should perhaps be directed toward making prepared milk or milk substitutes with adequate protein, mineral, and vitamin content for infant feeding, with secondary considerations to similar enrichment for bread or other staple foods consumed by adults and older children.

Increasing nutrition for lactating mothers and encouraging breast-feeding are logical courses that these studies suggest. This is perhaps the most practical way at present of protecting the young infant in many countries, since breast-feeding is still widely practiced. However, industrialization often brings with it a decline in the number of women who breast-feed their children, while those who do keep it up do so for a shorter time. For example, in Chile, one of the more rapidly industrializing countries, breast-feeding is rarely practiced and the infant mortality rate during the early months of life remains among the highest in South America.[33]

As developing countries begin to emerge into twentieth century patterns, they must anticipate these changes and protect their infants. If breast-feeding is abandoned, the problem becomes much more difficult. The population at risk will increase considerably. Supplying milk alone will not solve the problem. In Chile, where free milk is available, the government has increased the supply of powdered milk to infants 12-fold during the past 10 years. The infant mortality rate has not dropped even one per cent.[33] Why is supplying milk not solving the problem? Because it is impossible, under the conditions in which she lives, for the mother to prepare a sterile formula, because no refrigeration exists, or because the milk is given to the father or sold. The net result is that the infant gets a contaminated formula, contracts diarrhea, and the mother immediately stops the formula and goes back to the tried and true and cheap method of feeding the child a gruel made from flour and water—almost total starvation.

Perhaps the ready-to-drink formulas in this country could do the most good in developing countries where breast-feeding is on the decline. Perhaps other solutions are better. Suffice it to say, the population at risk is in most cases not the population for which major nutritional programs are launched. It may be cheaper in the short run to improve the nutrition of adults and older children. But in terms of over-all cost, it

would certainly be more efficient to use the available funds to protect the population most at risk and to prevent the exceedingly costly consequences of maintaining within the society large numbers of individuals who are unable to contribute because of marginal mental development.

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INTRAUTERINE GROWTH RETARDATION

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A number of variables influence the rate of growth in utero. A major one is gestational age. However, factors in addition to duration of pregnancy affect fetal size since the distribution of fetal weights at any given gestational age is relatively wide. Some degree of variation is inherent in normal biology but the lower extreme of this distribution contains a large proportion of fetuses whose growth has been impaired abnormally as a result of any of several influences. Only in comparatively recent times has the clinical significance of this pathological state come to be appreciated.

The condition goes under a variety of names--intrauterine growth retardation (IGR), fetal growth retardation, fetal malnutrition, dysmaturity--and the infants born as a result of it are called small for gestation age (SGA) or small for dates (SFD). Though some authors have differentiated between these various terms, there are no generally agreed-upon distinctions and they may be regarded as more or less synonomous. Similarly, standard definitions are lacking. Probably the most widely accepted standard employs the tenth percentile and below of birthweight for gestational age, although some have used the stricter criterion of mean minus two standard deviations. The incidence of IGR quite obviously depends on the diagnostic criteria employed. If the tenth percentile of weight for gestational age is used, one-tenth of newborns will be IGR by definition. If mean minus two standard deviations is utilized, the incidence (assuming Gaussian distribution) will necessarily be 2.5 percent.

Traditionally, all infants weighing less than 2500 grams at birth have been classified as premature. In recent years it has become increasingly clear that a significant proportion, usually about a third, of these low birthweight infants are actually mature by gestational age but for varying reasons have had impaired intrauterine growth. Differentiation of intrauterine growth retardation from prematurity is critical because the complications of the two conditions, and therefore the clinical approach, differ substantially. These differences in management apply to both fetus and newborn. Further, intrauterine growth retardation can result from any of a number of influences and determination of precise cause or causes, as best it can be determined, is essential for optimal results.

ETIOLOGIC CONSIDERATIONS

Conditions which are particularly likely to impair fetal growth can be classified in a number of ways. Probably the most logical approach involves classification according to factors primary in the mother, the placenta, or the fetus.

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Maternal factors

Of maternal conditions associated with fetal growth retardation, the most frequently recognized is vascular disease. Chronic hypertensive conditions and chronic renal disease represent classic causes. The duration of the condition and the level of the diastolic blood pressure appear to correlate independently with the likelihood of IGR. Of even greater prognostic significance is the presence or absence of demonstrable end-organ effects. For example, approximately half of patients with essential hypertension and secondary renal involvement manifest by proteinuria exhibit overt evidence of fetal growth impairment. A similar proportion of those with primary renal disease and secondary hypertension manifest fetal effects. The etiology of the hypertension or renal disease appears less important in fetal prognosis than its severity. Pregnancy complicated by diabetes mellitus can, in special circumstances, produce intrauterine growth retardation. While this condition in its milder form is classically associated with excessive fetal growth resulting in an infant large for its gestational age, severe and long-standing diabetes often eventuates in vascular disease which compromises fetal growth. Acute pregnancy-induced hypertension (pre-eclampsia-eclampsia) is less frequently a cause of intrauterine growth retardation. If truly acute, infants born with this condition are usually normally grown; however, if the process is superimposed on chronic vascular disease, fetal growth may have been impaired (14). Differentiation between the acute and superimposed varieties is sometimes difficult on purely clinical grounds. Indeed, recent evidence indicates that the onset of "acute pre-eclampsia" in late pregnancy is preceded by loss of the relative angiotensin sensitivity of normal pregnancy some weeks prior to the earliest clinical signs (9). Thus, acute pregnancy-induced hypertension may not be as acute a process as formerly thought. Nevertheless, when acute pre-eclampsia-eclampsia is accompanied by intrauterine growth retardation, consideration should be directed toward some underlying vascular disease.

A number of conditions characterized by hypoxia may limit fetal growth. It has long been appreciated that altitude is inversely related to birthweight and the mechanism presumably involves the lowering of oxygen content of the atmosphere with increasing elevations. Thus, pregnancy at high altitude may be associated with intrauterine growth retardation. The effect, however, is only a slight one at altitudes at which humans generally live. Substantially greater effects are likely with cyanotic heart disease in which the partial pressure of oxygen in the maternal blood is lowered. Patients with hemoglobinopathies, especially sickle cell disease, are often chronically hypoxic and pregnancy in such individuals typically produces growth retarded infants. Anemia by itself does not seem to have an appreciable influence on fetal growth, since maternal deficiency of iron or folate, even of a severe degree, is usually associated with infants of normal size.

Maternal nutritional status, certainly during pregnancy and probably preconceptionally as well, influences the rate of fetal growth. Numerous studies have substantiated the significant positive correlation that exists between maternal pre-pregnant weight and pregnancy weight gain on the one hand and infant birthweight and length on the other (20). The specific nutritional factors involved are not clear. Studies in experimental animals indicate protein to be the critical nutrient while those in humans point more to energy. This apparent difference may not actually be a difference at all; the well recognized metabolic interrelationships between energy and protein

dictate that adequate caloric intake is necessary for optimal protein utilization in order to prevent protein catabolism for energy. In any event, that protein-calorie malnutrition can cause retarded fetal growth has been amply demonstrated by studies of famines occurring in Holland and Russia during World War II. During the Dutch famine, mean birthweight fell by 300 grams and length, head circumference, placental weight behaved similarly (28). In Russia, the decline in mean birthweight was even greater (500 grams) and half of the infants born during the famine weighed less than 2500 grams (2). The relationship between malnutrition and fetal growth retardation is further confirmed by studies demonstrating a significant increase in mean birthweight with nutritional supplementation during pregnancy in populations of known or presumed deficient nutritional status (13). The third trimester seems to be the critical period for the effects of maternal nutrition on fetal growth.

Maternal cigarette smoking during pregnancy is associated with a decline in birthweight averaging 180 grams. The mechanism by which smoking causes retarded fetal growth is unknown but any of several factors could be responsible: relative hypoxia due to elevated blood carbon monoxide levels, placental transfer of a toxic growth-inhibiting substance, chronic vascular spasm of the uterine arteries, or appetite suppression in the pregnant woman. Recent evidence points to the nutritional influence as the predominant mechanism (25).

Placental factors

The etiologic role of the placenta in intrauterine growth retardation is a controversial subject. Based on the observed correlation between fetal and placental weight, the placenta is regarded by some as a primary regulator of fetal growth and placental abnormalities thought to be a frequent cause of growth retardation--hence the term "placental insufficiency" as a synonym for the condition. The other point of view regards the placental effect as usually secondary to the primary maternal or fetal factors impairing fetal growth. While careful histopathologic study of placentas from growth retarded fetuses reveals a high incidence of vascular and inflammatory lesions (1), such observations do not answer the question of whether the effects are primary or secondary. The majority opinion at present seems to support the latter and to consider primary placental causes as quite infrequent, though without doubt they can occur on occasion.

Shanklin, in a study of 6500 placentas (27), described four placental conditions associated with fetal growth retardation. Hemangioma of the placenta or umbilical cord is a very rare tumor which impairs fetal growth by mechanical interference with circulation through the placenta. Placental infarction when multiple and/or extensive ("diffuse fibrinosis"), can impair maternal-fetal exchange. However, only rarely is it of sufficient degree to exert a demonstrable effect and the very commonly observed small placental infarcts are without significance. The parabiotic transfusion syndrome with a monochorial twin placenta is rare phenomenon which results in overgrowth of one twin and undergrowth of the other. Finally, abnormal cord insertions can be associated with intrauterine growth retardation according to Shanklin. Other investigators disagree, however. In any event, abnormal cord insertions are quite common and only rarely (if ever) do they result in a growth retarded fetus.

Fetal factors

Chief among factors intrinsic to the fetus which may limit fetal growth are congenital malformations, particularly chromosomal abnormalities. Indeed, with the possible exceptions of the poly X and Klinefelter syndromes, some degree of intrauterine growth retardation is virtually universal in cytogenetic anomalies (24). The degree of retardation is most marked with trisomies involving the D group and the 18 chromosome. Somewhat lesser, but still clinically evident, degrees usually accompany other chromosomal anomalies. Other types of congenital abnormalities associated with fetal growth retardation include malformations of the alimentary tract which interfere with fetal swallowing (5). This association suggests that ingestion of amniotic fluid may normally provide a portion of the fetal protein requirement.

The other major category of fetal conditions causing growth retardation is chronic intrauterine infection (15). Rubella in both early and late pregnancy is frequently associated with intrauterine growth retardation and a specific growth-inhibiting substance produced by cells infected with rubella has been described (22). Similarly, cytomegalic inclusion disease, herpes infections, toxoplasmosis, and syphilis may, in some poorly understood manner, impair growth in the infected fetus.

Unknown factors

Theoretically, every case of intrauterine growth retardation should have a defined cause in mother, placenta, or fetus. However, it is not always possible to identify an explanation. Indeed, the incidence of "unexplained" fetal growth retardation has been found to be as high as 50 percent in some series (17). This figure is quite likely higher than necessary and could be lowered by careful systematic evaluation of the mother (for obscure vascular disease or malnutrition), the placenta (for subtle histopathologic abnormalities), and the infant (for subclinical infection or malformation). Nevertheless, even the most intensive investigation will leave a portion of cases as idiopathic. These may reflect a familial tendency to fetal growth retardation (16) or other causes as yet unrecognized. They may also simply reflect normal biologic variation in fetal growth.

DIAGNOSTIC CONSIDERATIONS

There are no specific diagnostic tests for pregnancy complicated by intrauterine growth retardation and therefore the condition can seldom be diagnosed prenatally with certainty. On the other hand, an index of suspicion can usually be aroused by careful attention to clinical factors and the birth of a previously-unsuspected SGA infant should be generally considered avoidable.

Underlying the diagnostic approach to intrauterine growth retardation is the concept, probably first expressed by Gruenwald (12), that fetal growth during the last half of pregnancy would be entirely linear if not limited by the supply of nutrients. Under normal circumstances, this supply is not sufficient to support unlimited growth during the last month of gestation and a decline in relative adequacy is reflected in the "flattening out" of the fetal growth curve beginning at 35 to 37 weeks. In abnormal states, the time at which the supply becomes inadequate for continued growth occurs earlier, resulting in

the clinical entity of fetal growth retardation. The degree of limitation determines the onset of retardation; the more severe the limitation, the earlier growth slows and ceases and therefore the more marked the effect at any subsequent stage of gestation. A classic case in point is that of multiple pregnancy in which at some point in late pregnancy the maternal capacity to supply nutrients or the placental capacity to transmit them nearly always becomes inadequate to satisfy the needs for normal (i.e., singleton) fetal growth. The greater the number of fetuses, the earlier the point of departure from normal growth.

Reasoning such as that outlined above quite obviously applies particularly to conditions extrinsic to the fetus (i.e., maternal and placental factors). Whether it also applies to intrinsic (i.e., fetal) factors is not known with certainty but most of the available evidence indicates that it does. A clinical corollary of this concept is that intrauterine growth retardation never occurs (or at least becomes clinically evident) prior to 20 weeks and seldom prior to 28 weeks. Thus, the most accurate method of diagnosis involves correlation of menstrual history with uterine size by a competent examiner in early pregnancy and then at some later time noting that fetal and/or uterine size is smaller than normal for the stage of gestation. A presumptive diagnosis of intrauterine growth retardation can and should be made in such a situation. The patient seen first in late pregnancy and noted to have a uterus smaller than anticipated on the basis of menstrual history represents a diagnostic dilemma. By careful observation and study it is usually possible to gain some idea of whether such a patient actually has intrauterine growth retardation or simply is earlier in pregnancy that the menstrual history indicates, but the distinction can rarely be made with certainty.

Certain anthropometric measurements are useful (7). Maternal weight, though admittedly a crude index, can be helpful. Static or falling weight usually accompanies intrauterine growth retardation; therefore, a normally progressive increase argues against the condition. Measurement of uterine height above the symphysis pubis should be done at each prenatal examination of all patients and static or falling values suggest fetal growth failure. However, there is considerable variation in uterine measurements from examiner to examiner and comparable data can only be derived from a single examiner using a standard technique. Somewhat greater precision is possible with measurement of abdominal girth at some reference point (such as the umbilicus). Changes in girth measurements relate fairly closely to changes in uterine size and much less influenced by extraneous variables such as different examiners.

Ultrasound scanning is a safe, non-invasive, and reasonably precise method of determining certain fetal measurements. The biparietal diameter is the most widely used and standard tables of biparietal diameter at various gestational ages are available (4). Such measurements done prior to 28 weeks relate quite closely to fetal age; after 28 weeks, the reliability of a single study is lessened substantially, presumably because of the prominence of factors other than age that can influence fetal growth during the last trimester (26). Serial ultrasound studies provide the opportunity to evaluate growth of the fetal head by comparison with tables of normative data. The growth rate of the fetal head normally shows more or less progressively during the last half of pregnancy and from data such as these it is readily possible to determine in a particular case if growth is abnormally slow. Serial studies should

generally be done at no less an interval than two weeks, or perhaps three weeks in the last month of pregnancy (6), since the precision of the method is such that measurements of 1 to 2 mm difference can probably not be differentiated from each other with confidence.

Amniocentesis can be helpful in several ways. In the first place, merely being able to obtain amniotic fluid can be significant. Since the success rate of amniocentesis is related to amniotic fluid volumes and since oligohydramnios often accompanies intrauterine growth retardation, aspiring fluid with ease, particularly if the fluid is clear, speaks against severe fetal involvement. On the other hand, unsuccessful amniocentesis or fluid containing meconium enhances the possibility of compromised fetal status. Amniocentesis also permits analysis of the fluid to estimate gestational age and, more specifically, fetal maturity. Interpretation of the amniotic fluid indices of fetal maturity is discussed in detail elsewhere in this book. Finally, amniocentesis provides the opportunity to examine potential fetal causes of growth retardation. While rarely would amniocentesis be done sufficiently early to permit use of karyotype determination from chromosome cultures, amniotic fluid can be cultured for microbial organisms and the information obtained might have clinical significance. For example, if a patient with genital herpes had a positive amniotic fluid culture, the fetus must be considered to be involved. If, on the other hand, the amniotic fluid culture were negative for herpes, delivery by Cesarean section should be employed to minimize the risk of fetal infection with parturition.

Endocrine and other tests on maternal blood and urine have only a limited place. Estriol, a hormone produced by a series of biosynthetic mechanisms in the fetus and placenta, is widely employed as an index of feto-placental function. Levels in urine or plasma relate to fetal size, among other parameters (18). However, estriol is of little worth in the diagnosis of intrauterine growth retardation since a given level does not permit differentiation between a growth retarded and a premature fetus (3). It may have some value in following a patient once the diagnosis is made (29). Human placental lactogen (HPL) levels in the maternal serum correlate with placental weight but again a given concentration does not differentiate between growth retardation and prematurity. Serum oxytocinase and heat stable alkaline phosphatase are generally low in intrauterine growth retardation but there is substantial overlap with the normal range, limiting clinical usefulness (21,23).

MANAGEMENT

At risk for IGR

The patient at risk for intrauterine growth retardation might be a woman with known hypertensive or renal disease, cyanotic heart disease, a past history of an SGA infant or obvious poor nutritional status. Hopefully, such a patient would be seen early in pregnancy for correlation of menstrual history and uterine size. The initial evaluation should include a careful assessment of nutritional status and detailed dietary advice consistent with recognized nutritional standards for normal pregnancy (8). This aspect of management is important in order to eliminate, insofar as possible, malnutrition or a cause of fetal growth retardation.

Prenatal examinations should be scheduled at intervals of two or three weeks, rather than the customary four weeks. Each visit should include careful and accurate measurement of body weight, uterine height, and abdominal girth and brief re-assessment of nutritional status.

Ultrasound cephalometry should be carried out during the interval of 20 to 24 weeks and repeated at a minimum at intervals of 6 to 8 weeks. If all of these studies--maternal weight gain, uterine growth and fetal head enlargement--follow the normal pattern to term, delivery of a normally grown infant may be anticipated with reasonable certainty. Deviation from the normal pattern in any parameter calls for more careful attention.

Suspected IGR

The patient in whom fetal growth retardation is suspected, whether or not any predisposing causes are known, should be examined at weekly (or less) intervals. Serial measurements of weight, uterine height, and abdominal girth should be made at each visit. An ultrasound scan should be done at the first suspicion of intrauterine growth retardation and repeated (usually) two weeks later to assess growth of the biparietal diameter. Amniocentesis should be at least considered and, depending on the degree of suspicion, carried out to estimate gestational age and rule out oligohydramnios and meconium passage.

Criteria for the diagnosis of intrauterine growth retardation include a significant disparity between uterine size and menstrual history (assuming the latter to be reliable), failure of uterine height, abdominal girth, and estimated fetal weight to increase over the course of one month, and failure of fetal head growth by ultrasound cephalometry over two weeks.

Diagnosed IGR

The patient in whom a diagnosis of IGR is made should be managed in accordance with a carefully designed program. Physical activity should be limited and she should spend defined periods (e.g., two hours two or three times daily) at bedrest in the left lateral position for the purpose of improving uterine blood flow. Hospitalization may be necessary if circumstances preclude this type of activity limitation at home. Amniocentesis should be done for the reasons outlined earlier and serial estriol levels in plasma or 24 hour urine collections measured. Ideally, estriol determinations should be done daily; at the minimum, the frequency should be two or three times per week. Interpretation must take into account the rather wide variation that apparently occurs normally. The level of significance in falling estriol values needs to be defined by each clinic and laboratory involved but in general decline must be more than 30 percent to be considered significant. Moreover, caution should be used in assigning significance to a single determination and as many as five values may be required (18). With these qualifications, fetal jeopardy may be indicated by a substantial decline or a significant downward trend in estriol values.

The oxytocin challenge test or contraction stress test, a new means of fetal assessment (10), appears quite useful in intrauterine growth retardation. It involves induction of uterine contractions by intravenous oxytocin with external electronic monitoring of the fetal heart rate--uterine activity

relationships. Its principal value is negative in nature in that fetal death rarely occurs within a week of a normal test (i.e., one without periodic heart rate decelerations). Thus, a normal test gives reasonable assurance that the fetus will not die within a week. The significance of a positive test is less clear; it does not necessarily presage intrauterine death but only means that fetal well-being can no longer be assumed. A patient with known intrauterine growth retardation should have an oxytocin challenge test at the time of diagnosis and the test should be repeated weekly as long as negative.

Delivery should be considered under two general circumstances: (1) evidence suggesting fetal jeopardy (e.g., significant decline in estriol levels, meconium in the amniotic fluid, or a positive oxytocin challenge test) at or after the thirty-fourth week of gestation, or (2) persistent growth failure (e.g., static fetal biparietal diameter on ultrasound scan) with unequivocal evidence of fetal maturity during the last month of pregnancy. Amniotic fluid indices of fetal maturity, particularly pulmonary maturity, play a central role in the timing of delivery (19).

The proper method of delivery in intrauterine growth retardation is a matter of some controversy. In view of an increased likelihood of intrapartum fetal death with maternal and placental causes, apparently because uterine contractions are accompanied by intermittent impairment of an already marginal uterine blood flow, some have advocated routine Cesarean section. Such an approach may involve subjecting the pregnant woman to the hazards of abdominal delivery for a congenitally malformed or infected infant with little or no likelihood of normal existence. Fetuses who are growth retarded because of intrinsic fetal causes generally tolerate labor satisfactorily, so the preponderance of opinion favors a trial of labor in most or all instances of intrauterine growth retardation. This trial must be conducted under strictest observation, utilizing modern methods of continuous electronic monitoring of the fetal heart and uterine contractions supplemented by fetal blood gas studies as indicated. As long as these indices remain normal, labor is allowed to progress and vaginal birth is anticipated. Deviations from the normal indicating fetal hypoxia should be dealt with promptly, which in most instances means delivery by Cesarean section.

A specific instance in which a trial of labor might be avoided is that in which the oxytocin challenge test is positive. However, even under these circumstances a trial of labor is probably advisable, assuming careful monitoring is possible, since some 25 to 40 percent of fetuses with a previously positive oxytocin challenge test tolerate labor without incident.

The newborn who is small for gestational age is subject to a number of complications discussed elsewhere in this book. One of particular importance because of the need for management immediately after birth is meconium aspiration. Meconium in the amniotic fluid--traditionally regarded as a sign of fetal distress but a non-specific sign at best--may be aspirated by the fetus, particularly in response to hypoxia. Any instance in which meconium has been passed in utero should be managed by endotracheal suction immediately upon birth. By this aggressive approach the incidence and severity of the meconium aspiration syndrome can be reduced significantly (11).

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NEONATAL ASPECTS OF AN "INTERDISCIPLINARY APPROACH TO ADOLESCENT PREGNANCIES"

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Pregnant adolescents are a group at high risk for complications of pregnancy. However, except for those who are very young (less than 15 years old), other factors such as race and socioeconomic status may be more important determinants of obstetric complications than is age alone (1). In addition, the interval between onset of menses and conception may be more closely correlated with obstetric complications than is age alone. That is, the frequency of low-birth-weight infants increases as the interval between menarche and conception shortens (2).

The major neonatal hazards of adolescent pregnancy are:

1. Low birth weight (less than 2500 gms). This group includes infants born prematurely and infants who are small-for-gestational age due to intrauterine growth retardation (IUGR). The incidence of low-birth-weight infants is significantly increased in pregnancies of women under 20 years of age. The percent incidence varies with the population studied, but has been found as high as 18-27% in poor, black women (3,4). Specific therapeutic problems presented by the two subgroups of low-birth-weight infants are:

   A. Prematures. This group presents the major therapeutic challenge because most of the increase in perinatal mortality in adolescent pregnancies is due to prematurity. The problem of pulmonary immaturity, with resultant hyaline membrane disease, is a major concern. Other problems of immaturity -- feeding difficulties, poor temperature control, irregular respirations, jaundice -- are also important concerns, their severity depending on the degree of prematurity. Adequate care of premature infants requires sophisticated equipment, nursing and medical care which are now available in neonatal intensive care units.

   B. Intrauterine growth retardation. Infants with this problem probably make up 30-50% of the low-birth-weight infants born to adolescent mothers. However, many of the published series fail to distinguish prematurity and IUGR so the frequency is uncertain. Newborns with IUGR, if born close to term, will not show most of the problems of immaturity listed above, but can have early problems with hypoglycemia. This must be prevented by anticipating its occurrence, monitoring blood sugars frequently, and by starting oral and/or parenteral feedings in the first hours of life. The more severely affected infants with IUGR may show later problems in physical growth and in mental-motor development which cannot be attributed to early hypoglycemia. Rather, the nutritional limitations during fetal life may result in an inability to catch up later in physical and mental growth.

2. Toxemia. The other major complication of adolescent pregnancy is toxemia (high blood pressure, proteinuria and edema). This can be seen in pregnancy at all maternal ages but is significantly more common in first pregnancies and in adolescents. This problem carries both maternal and fetal risks, with early delivery of a premature infant frequently necessary to prevent severe maternal illness. Toxemia is characterized by reduced uterine and

placental blood flow, resulting in frequent undernutrition of the fetus and IUGR. Thus, the neonatal hazards of prematurity and of IUGR are found secondary to toxemia. In addition, such fetuses may tolerate the stresses of labor and delivery poorly and thus they are at high risk to be severely depressed at birth. Adequate care of both the mother and infant require very good and frequent prenatal care, supervision of labor and delivery in an obstetric unit specially equipped and staffed for high-risk pregnancies, and ready availability of sophisticated pediatric care in an intensive care unit, if necessary.

How can these obstetric and neonatal hazards be avoided?

A. Excellent prenatal care can lead to early identification of toxemia and permit institution of therapy so that the pregnancy can continue to the point where fetal and neonatal risks are low.

B. The efficacy of nutritional supplementation in reduction of incidence of toxemia is in much dispute. The possible beneficial effects of nutritional supplements in increasing birth weight are being studied at present (5,6). A recent report indicates that significant benefits can be gained (6).

C. Active counselling on birth control methods should be carried out during the prenatal visits. When a decision can be made on a birth control method before the infant is born, there is an increased probability of it being used post-partum (4).

D. Adolescent pregnant women should be considered high risk and should be delivered in high-risk perinatal centers where the conditions are optimal for care of the mother and her high-risk newborn infant.

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INTERDISCIPLINARY APPROACH TO ADOLESCENT PREGNANCIES--MATERNAL

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Numerous studies indicate that obstetric performance of the adolescent patient is not optimal. Some series report a higher incidence of contracted pelvis, anemia, prolonged labor, and premature labor. Conflict exists with respect to many complications because of the diversity of socioeconomic and age groupings in the reported series (1). However, several obstetric complications of adolescent pregnancies are well-documented. Infants born to adolescent mothers are more likely to be of low birth weight with a significant number having infants weighing 2500 grams or less (2). Secondly, toxemia of pregnancy appears more frequently in pregnant adolescents with the increase being progressive for each year of age under 20 (3). Most investigators further agree that the youngest patients, particularly those under 16 years, and the non-white population experience greater numbers of complications. In addition to obstetric or medical problems, adolescents are likely to experience repeated out-of-wedlock pregnancies. Sarrel and Davis reporting on a 5-year followup of 100 teenage pregnancies note that 95 had subsequent pregnancies producing 340 offspring (4). In light of the obvious need for services to the adolescent pregnant patient, diverse community programs have been developed in an effort to provide comprehensive care to this group. As noted by Howard, the goals of a program are: 1) early and consistent prenatal care, 2) continuing education, and 3) individual or group counseling (5).

Intensive prenatal care utilizing an interdisciplinary approach and intrapartum surveillance of the fetus, as well as advances in newborn care may serve to diminish medical complications occurring in the adolescent. Utilizing an interdisciplinary approach with a medical model, Sarrel reports favorable obstetric results, and a marked decrease in the incidence of subsequent pregnancies in this group (6). His program, in a university setting, involved social workers, psychiatrists, nurses, public health workers, pediatricians, as well as members of the obstetric staff. The obstetrician may play a significant role in organization and support of such a program, and is in a unique position to offer direct supportive and specialized care, both prenatally and during the intrapartum period. In addition, contraceptive care and followup may be emphasized.

Locally, Dr. Laura Edwards, director of the St. Paul Maternal and Infant Care Project, reports a decrease in teenage pregnancies following institution of a teenage OB-Gyn Clinic operating within a local high school (7). Counseling and care are offered by nurses, social workers, nutritionists, dental

hygienists, and home economists in addition to a physician. It is clear that the success of this unique program is related to the setting in which the program is instituted.

For many years, the Pilot City Regional Health Center has provided obstetric care for a high-risk population many of whom are adolescents. The program is based on a strong nursing program with emphasis on factors which relate to high-risk pregnancies. Under this setting, an interdisciplinary approach is utilized, with ready access to nutritionists, mental health workers, social workers, public health nurses, and other specialized medical services. Supervision and overall patient management is provided by an obstetrician. Patients at risk are then referred to Hennepin County Medical Center, and all patients deliver at this institution. A substantial percentage of the population is adolescent. However, the main thrust of the counseling is through individual counseling by highly-trained nurses. The framework for a more highly-organized, specific adolescent program exists. A similar program of care is administered through the Maternity Clinics of the Minneapolis Health Department.

A special education program for pregnant school girls is maintained locally at Holmes School while medical care is obtained elsewhere. Educational and social services are provided as well as the services of a public health nurse. There is a 67 per cent continuation rate in the school program, and obstetric outcome in this group appears favorable (8).

Recently, a locally-funded project initiated by the Childbirth Education Association of Greater Minneapolis and St. Paul, and termed Project Outreach, has attempted to reach the disadvantaged patient through prepared childbirth education classes. It has been demonstrated that these classes do reach significant numbers of pregnant adolescents, and patients in lower socioeconomic groups (9). The program's main value is its attempt to offer prenatal education to a disadvantaged group. Further, although the setting of the classes has been primarily within a medical institution, poor, single or young private patients are encouraged to participate.

Some of the programs described above have attempted to reach the disadvantaged patient, many of whom are the adolescent age group. However, formal interdisciplinary approach specifically directed towards the adolescent patient has been lacking. Of 2,621 deliveries at Hennepin County Medical Center between January 1973 and August 1975, 275 or 10.4 per cent were born to mothers age 17 or under. Coordination of existing programs to further meet the needs of these patients, and to prevent repeated pregnancies in this age group may be possible.

Problems exist as to reaching the adolescent pregnant patient in the rural environment, and those adolescent patients in the private medical community who need specialized services. Independent programs, such as that described for the Outreach Program, may serve as a model for specific programs relating to the adolescent pregnant patient.

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SERVICES AND PROGRAMS FOR THE PREGNANT ADOLESCENT AND HER INFANT

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There are a variety of nutrition and home economics programs available to pregnant adolescents and their infants in our six state area. Some of the best known are the Nutrition Services available in the Maternity and Infant Care projects of which there are seven in our region: one in Minneapolis, and one in St. Paul. These services include a nutrition assessment to determine nutrition, dietary or food resource problems, nutrition and dietary counseling, other therapeutic nutrition services, referrals for food resources, and often group education.

Some of our projects have additional nutrition or nutrition related services such as the Minneapolis "Homemakers for Health" program. This is a consumer education program for project clients which includes a great deal of nutrition and food education. The classes are held in three churches in low socio-economic areas served by the project. Clinics are held in the same locations. The Minneapolis Area Vocational School provides home economics teachers for the project. A community aide from the Minneapolis Health Department and a program aide from the Hennepin County Extension Office recruit participants for the classes and assist with instruction when appropriate. They also work with the families to help them implement at home the ideas learned in the class and since there is a local Expanded Nutrition Program, with the Extension Service, families needing in-depth assistance with food buying or food preparation can receive this help. The churches furnish transportation, baby sitting services and the meeting facilities. The program is coordinated by the Maternal and Infant Care project Home Economist.

Another local program offering special services to the pregnant adolescent and her infant is also an offshoot from a Maternal and Infant Care project. This is the St. Paul Mechanics Art High School program which joined forces with the Maternal and Infant Care project to develop a comprehensive program of health services, education, and day care. Health services cover prenatal and postpartal care which includes comprehensive nutrition services, pregnancy testing, V. D. testing and treatment, pap smears, birth control counseling and referral for other services, immunizations, preventive dental services, athletic physical examinations and weight reduction classes.

The day care center opened in December, 1973. Its primary objective is to allow the adolescent parents to complete high school and at the same time learn good parenting skills by working with their infants in the center. An important part of this is learning the food needs of their infants and good infant feeding practices.

A series of thirteen classes is jointly taught by the Home Economics teacher and Maternal and Infant Care project staff to the student parents. In addition to covering routine prenatal topics such as nutrition and preparation for child birth, some of the sessions focus on the adolescent's feelings and attitudes toward child rearing and parent-infant inter-actions.

There have been changes in the school curricula strengthening nutrition, health, and sex education in grades seven and eight. The Home Economics teacher teaches a class called "Exploring Childhood" and the project has been instrumental in getting a required quarter of health education for all tenth graders which includes sex and nutrition education as part of the curriculum. Weight control classes have been implemented with the physical education instructors and have been enthusiastically received. The most recent curricula addition has been on drug abuse and the school now offers individual and group counseling and referral services for students with potential or actual drug abuse problems.

Evidence of the broad acceptance of the program is the fact the total health, education, and day care project has been included in plans for the new high school which will absorb students from Mechanics Arts school. The new facility will be completed by 1977 and will have an expanded health clinic, a large day care/nursery school facility and classroom space for child development classes.

One final local program is the Minnesota Supplemental Foods Program for Women, Infants and Children (WIC). In 1975 the Minnesota legislature created and funded at the level of one million dollars a state WIC program that will extend the Federal WIC program into additional communities. This program will make specific nutritious foods available to prenatal and lactating women, infants, and children through 3 years of age in low-income areas. Receipients must be receiving health care through a local health agency and must be designated as nutritionally at risk. The program is administered by the State Health Department which will begin implementing the program as soon as the regulations are finalized.

Cincinnati General Hospital is the setting for an Infant Stimulation program. This program is sponsored by a multitude of agencies and organizations including the local health department, General Hospital, Children's Psychiatric Center, the Maternity and Infant Care Project, Cincinnati Maternity Society, Babies Milk Fund Association, the Office of Economic Opportunity, etc. These groups have been working together to enrich the development and improve the quality of life of infants of poverty level mothers through a group training program directed toward the mothers combined with comprehensive health services for the infant. The project has three components: A Mother Training Component, a Medical Component and a Nutrition Component.

Some of the stated objectives of the project are to train disadvantaged mothers to implement an educational curriculum with their infants at home; to foster the sensory-motor, cognitive, and language development of disadvantaged infants; to develop a sense of dignity and worth in poverty mothers as they demonstrate self-help capabilities; to provide a setting where family problems beyond the mother-infant focus can be openly discussed; to replace crisis-oriented medical programs with comprehensive health and education services to increase the mother's awareness of the health needs of her infant through ready access to health services; and to increase the mother's awareness of the nutritional needs of her infant and intensify her concern for supplying proper nutrition to her infant.

Mothers attend weekly two-hour training sessions where they are taught to implement sequential learning skills with their babies. The project coordinator visits the mothers in the home to informally assess the mother's progress and to continue the training process begun in the classes. The mothers keep a daily log of the baby's sleeping pattern, feeding schedules and stimulation activities carried out during the day. The mothers bring their families to class every two weeks where they demonstrate their teaching skills with the use of stimulation materials, most of which are made by the mothers themselves. The project coordinator serves as a teacher model and a reinforcer of appropriate mothering behavior.

The infants receive comprehensive medical and health care and health education through the hospital and the health department or the Maternal and Infant Care project clinics. In addition to the nutrition services provided in the clinic, the Maternal and Infant Care project nutritionists participate in the mothers classes, helping the mothers understand the nutritional needs of their infants in relation to growth and development, how to develop good food habits in their infants and their own nutritional needs and how to meet them. The mothers participate through such activities as keeping food intake records on their infants, planning adequate and appropriate menus, weighing and measuring their infants and plotting their weights on growth charts and preparing nutritious snacks for the children.

The project staff have seen improvement in the positive mother/infant interreactions and have seen low birth weight infants make excellent weight gains. They believe they have shown that the setting for this social, educational and health program within a busy pediatric clinic in a hospital is both a natural and an effective setting for such a program.

The Infant Intensive Care Center at the University of Indiana Medical Center is working with the State Health Department to develop a regional perinatal care program to serve the high risk prenatals and infants in a large area in the central part of the State. The Pediatric Dietitians have been providing nutrition consultation to the Intensive Care unit for several years and with the development of the more comprehensive perinatal program are developing a more adequate role for the pediatric dietitian who will be functioning in all aspects of the perinatal program. This will include providing nutritional guidance to the high risk mothers prior to delivery, consultation to the perinatal and intensive care unit staffs on nutritional care of the high risk infant, nutrition counseling of parents of the infants on appropriate care of the infant who may be of low birth weight or may have a chronic condition such as cerebral palsy, congenital heart disease, myelomeningocele, or cystic fibrosis and who need specific nutrition counseling. The dietitian will continue to give guidance to the parents as they bring the child back to the medical center to the special clinics for continuing care. In addition, with the assistance of the State Health Department nutritionist they will identify community nutrition resources throughout the perinatal region that can be used as referral resources in the local communities where the mother and infant reside.

The perinatal project dietitian will also provide in-service education and training for these community resources, for smaller hospital (perinatal level 2) personnel who will be giving some service to these high risk mothers and infants and to the various students in medicine, nursing, dietitics, and social work at the University.

SOCIAL, SOCIAL-PSYCHOLOGICAL AND PSYCHOLOGICAL APPROACHES TO ADOLESCENT PREGNANCIES

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A review and abstracting of the published literature on pregnant adolescents was done for the years 1960-1970, (Baizerman, et al, 1971). Then a critique was done of this literature, with the focus primarily on published research. (Baizerman, et al, 1974). These findings will be reviewed here as a basis for description and discussion of more recent research.

Several papers and texts have appeared (or are forthcoming) since 1970. Many of these are by authors who have published widely. These were reviewed; and select findings will be noted.

Community-based service programs continue in the U.S. (Baizerman, 1972 and Baizerman, et al, 1972). Some issues defined by practitioners will be noted also.

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