

## REPRINTS AND REFLECTIONS

# Biological Freudianism

## Lasting effects of early environmental influences

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... the childhood shews the man  
As morning shews the day ...  
JOHN MILTON  
*Paradise Regained*

### Social determinants of growth and health

As commonly used, the phrase 'early influences' denotes the conditioning of behavior by the experiences of very early life. Early experiences, however, do more than conditioning behavioural patterns; they also affect profoundly and lastingly many biological characteristics of the adult. I shall show that, in animals, events occurring during the very first days of life determine the initial growth rate, the maximum adult size, the efficiency in utilization of food, and the resistance to infection, malnutrition, and other stressful stimuli.

Early influences are, of course, at least [as] important in human life as they are in animal life. In fact, the experiments to be reported here were designed to provide experimental models for the study of socio-medical problems first recognized in human populations.

During the past century, for example, there has been a constant trend toward earlier maturation of children. This phenomenon was first detected in the United States, then in other Westernized countries; it is now particularly striking in Japan. Evidence for earlier maturation is provided by the greater heights and weights of children at each year of age; by the faster growth rates during adolescence for both boys and girls; and by the earlier age of the first menstrual period. In England for example, the menarchal age was  $15\frac{1}{2}$  for the well-off townspeople in 1820, whereas it had fallen to 13 in 1960.<sup>1</sup>

Needless to say, the trend towards earlier maturation cannot be extrapolated far back in time. In fact there is evidence that the menarchal age was 14 in Shakespeare's time, at least in the favored social classes.<sup>2</sup> The beginning of the nineteenth century apparently corresponded to a low ebb in the rate of physical and sexual development, perhaps because of the poor health conditions that prevailed at the end of the Napoleonic wars and during the early phases of the Industrial Revolution. What is certain in any case is that changes in the environment and in

the ways of life during the past century have been associated with a marked increase in the growth rate of children throughout the Westernized world.

The fall in mortality caused by diarrhea, tuberculosis, and other respiratory diseases during the past century in the United States and in other prosperous countries provides a spectacular illustration of the direct relationship that exists between high living standards and increase in resistance.<sup>3,4</sup> There is overwhelming evidence, furthermore, that the fall in mortality has been especially marked among the young age groups (Figure 1).

I shall not discuss the mechanisms of the fall in infantile mortality but shall emphasize instead that the essential cause of the improvement was greater resistance to disease, rather than control of pathogens or more effective medical treatment. The increased resistance to disease was brought about by social advances.

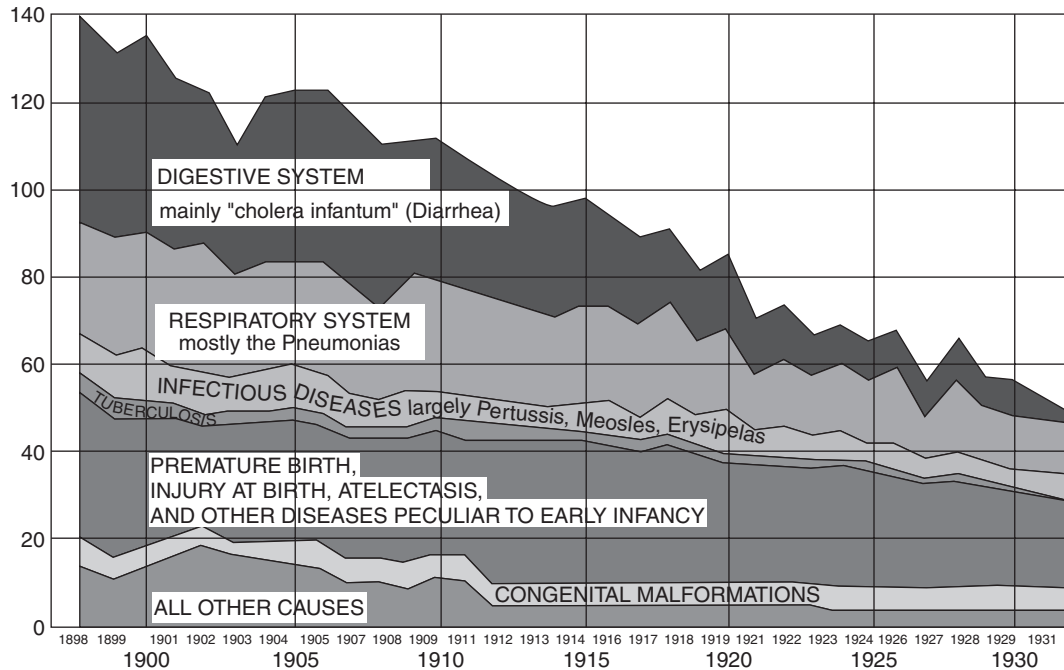
The influence of social factors on growth and health has been particularly well documented in the countries of Central America. Very high infant mortality, slow rate of growth during childhood and adolescence, and physical and mental lethargy continuing throughout life are among the pathological manifestations common to all the deprived social groups of Central America. These disorders are not racially determined; they are found alike among the deprived Indians and among the populations of European origin who share their ways of life. In contrast, these disorders are rare among Indians and Latin people born and raised in social and economic environments similar to those now prevailing in the United States and in Europe.

While it is thus certain that physical and mental development, as well as physical and mental health, are profoundly influenced by social factors, the complexity of the interplay between man and his total environment has handicapped the epidemiological and clinical study of such socio-medical problems. My purpose in the present report is to show that it is possible to create laboratory models useful in the study of human population problems. I shall emphasize in particular some of the lasting biological effects of early environmental influences.

### Indigenous microbiota, growth, and food utilization

The development in our laboratory of models illustrating the effects of early influences was facilitated by the results of our earlier investigations with three mouse colonies that have the

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**Figure 1** Infant mortality by prominent causes. Rates per 1000 births; New York City. (New York City Department of Health.)

same genetic origin yet differ widely in several important biological characteristics.<sup>5-8</sup>

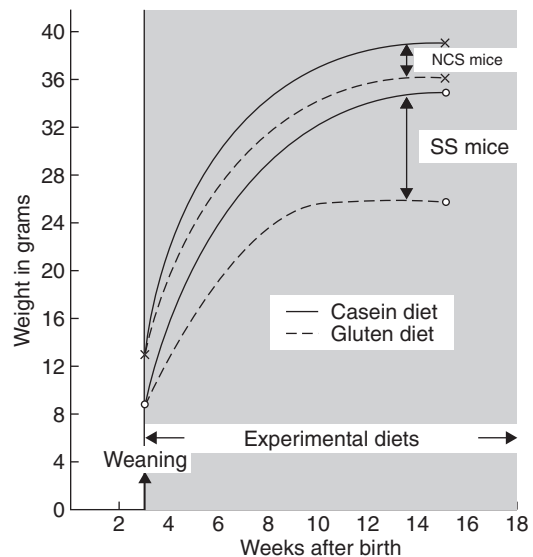
The colony of so-called standard Swiss mice (SS) has been maintained at the Rockefeller Institute (now Rockefeller University) for more than 50 years. The CFW colony was originally derived from the SS colony but has been in commercial production outside New York. The NCS colony was developed at the Rockefeller Institute 8 years ago out of nine animals obtained by Cesarean section from SS mice. Attempts have been made to maintain the NCS colony in a pathogen-free state at the Rockefeller University; a subcolony of it (NCS-D) has been continuously bred under semi-protected conditions in our own laboratories for the past 8 years.

As reported elsewhere, the mice of the NCS colony, and especially of the NCS-D colony, differ profoundly from SS and CFW animals. Figure 2 illustrates differences in weight at weaning time, in growth rates of the young, in the size of the adults, and in nutritional requirements.

In the experiment illustrated in Fig. 2 all animals had been fed the same natural diet before mating as well as during gestation and lactation. Yet, the young of the SS (or CFW) animals were smaller than those of the NCS animals at weaning time. The difference in size between these two groups persisted from then on, irrespective of the composition of the diet the animals received after weaning.

The difference between the SS (or CFW) and NCS animals becomes even more striking when the diet is inadequate. This is apparent in Figure 2 for the animals fed the wheat gluten diet (low in lysine and threonine). The NCS mice continued to gain weight on this amino-acid deficient diet, but, in contrast, the SS animals failed to grow altogether, or at best remained abnormally small.

Earlier studies have revealed that the difference in efficiency of food utilization between NCS and SS (or CFW) mice is not



**Figure 2** Comparative growth rates of SS mice and NCS mice. All animals were born of mice fed a mixed natural diet (commercial pellets D & G) during gestation and lactation. Newborns were fed either casein diet or wheat gluten diet after weaning

genetically determined; rather, it is an expression of the different microbiota acquired by the animals during early life. The influence of the indigenous microbiota will not be discussed further at this time because the effects of early influences have been more sharply defined in other types of experiments now to be described. The general principle of these experiments was to introduce a variable of short duration during early life and to observe the delayed consequences of this intervention in animals that were maintained thereafter under optimum conditions.

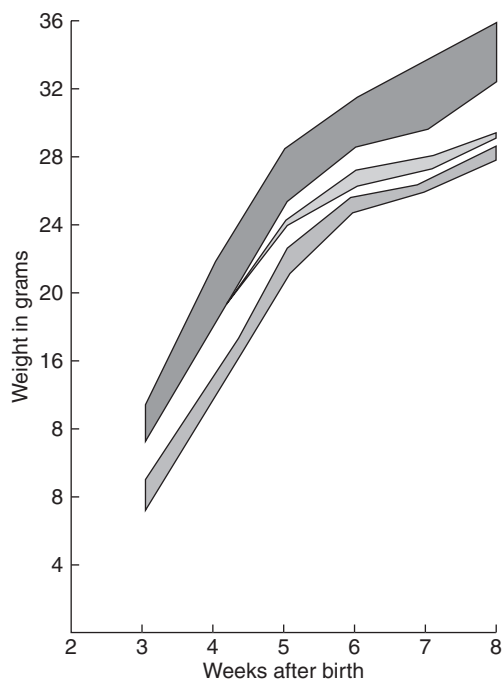
### Foster mothering, weaning weights, and adult size

Despite the long inbreeding of the mouse colonies just described, and despite all efforts to standardize the breeding conditions, the litters exhibit marked differences in weaning weight, in growth rate, and in adult size. It was thought at first that these differences were due to the genetic constitution of the individual mice. For this reason, an effort was made to render the distribution of physical characteristics more uniform by pooling all the newborn animals and reallocating them randomly to foster mothers. The results of this pooling and random allocation, however, were very different from what had been expected. They showed that the growth characteristics of the newborn animals were highly uniform for each foster mother, but differed markedly from one foster mother to the other. In other words, individual variability had its origin not in the genetic endowment of each animal, but in the nursing effectiveness of the mother.

In one particular experiment, 240 mice born the same day were separated from their mothers 2 days after birth and pooled. They were then reallocated randomly to these mothers, each of the latter receiving eight young. All foster mothers accepted the eight young, which grew normally. Figure 3 presents a typical group of results for three mothers.

It will be noticed that the weaning weights of the young animals fell within a narrow range for each particular group. Furthermore, the relative order of weights of individual animals remained the same after they had been separated from their foster mothers and fed thereafter the same diet in the same room.

In another experiment, the newborns were randomly allocated to foster mothers approximately 18 hours after birth. Table 1 shows their weight at that time and their subsequent



**Figure 3** Newborn NCS mice pooled, then randomly allocated to three foster mothers on second day of life (8 per mother). All animals fed mixed natural diet (commercial pellets D & G)

rates of growth. It will be seen that the nursing effectiveness of the foster mother became apparent within a very few days and that its effect on the relative weight rank of the newborns persisted thereafter.

The design of the two preceding experiments rules out that the groups of animals differed because of their genetic constitution, since they had been pooled and randomized; moreover, the differences among the groups did not have a prenatal origin, since the animals had been randomized after birth. All differences shown in Figure 3 and Table 1 could be traced, therefore, to the influence of the foster mothers during lactation. Quantity of milk, quality of milk, or other more subtle behavioral attributes of the foster mother account totally, or in part, for the differences in growth rates of the young. What is certain in any case is that the early experiences derived from the nursing mother had conditioned the development of the animals not only during lactation but also probably for long periods thereafter, and probably for their whole life span.

### Nutrition of the lactating mother and growth of the young

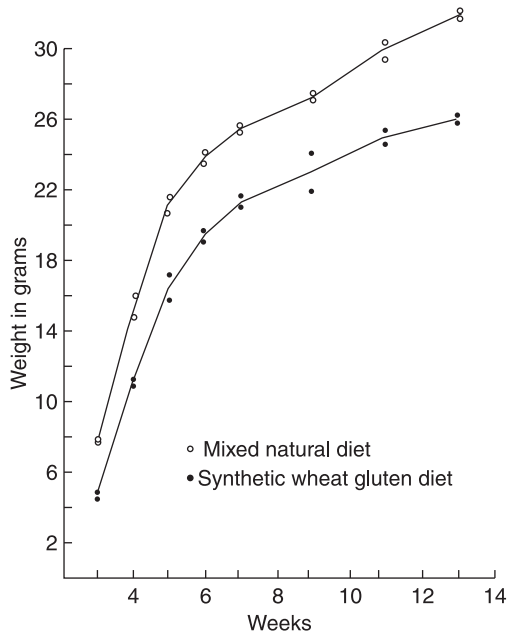
The general improvement in child nutrition certainly accounts in large part for the acceleration of physical growth and of sexual maturity that is occurring everywhere in affluent societies. There is much reason to believe that the very early nutritional influences are particularly important in this regard. The following experiments illustrate that, in animals, the nutritional state of the mother during lactation affects not only the initial rate of development of the young but also the final stature of the adult.

Pregnant NCS female mice were placed on various experimental diets just before delivery and were maintained on

**Table 1** Effect of foster mother<sup>a</sup> on neonatal growth of NCD-D mice<sup>a</sup>

Foster mother	Individual weights at indicated days (g)			
	1	4	8	11
A	1.4	2.8	5.0	7.4
	1.4	2.8	5.2	7.9
	1.5	2.8	5.2	8.0
	1.5	2.8	5.4	8.1
	1.5	2.9	5.4	8.1
	1.6	3.1	5.6	8.1
	1.8	3.2	5.7	8.2
	1.8	3.3	5.8	8.4
	B	1.5	1.8	3.6
1.5		1.9	3.6	6.3
1.5		2.0	3.7	6.4
1.7		2.0	3.9	6.6
1.7		2.0	4.0	6.6
1.8		2.2	4.1	6.7
1.8		2.8	4.9	7.7

<sup>a</sup> NCS-D mice, 7 weeks of age, gave birth the same day. All newborns were pooled and reallocated randomly to these NCS-D mothers 1 day after birth, eight per foster mother. The table presents results for two foster mothers having received young which were comparable in initial weight.



**Figure 4** NCS female mice fed either mixed natural diet (commercial pellets D & G) or synthetic wheat gluten diet from the time of delivery and throughout lactation period (0–21 days). All newborns fed D & G pellets after weaning at 21 days of age (two groups of 12 mice each; 0–14 weeks)

these diets throughout the lactation period. Their young were weaned at 3 weeks of age and from then on all were fed the same mixed natural diet (commercial pellets D & G). In other words, the differences in nutritional regimen were limited to the mother and to the period of lactation.

The experimental regimen of the pregnant animals in one particular experiment consisted of a semi-synthetic diet containing 20% wheat gluten (supplemented with cysteine) as sole source of protein. The diet was, therefore, low in lysine and threonine but was otherwise adequate with regard to all growth factors known to be essential for the adult mouse. The young of females fed this gluten diet were compared with those of females fed the complete natural diet (D & G pellets).

As will be noted in Figure 4 the young produced and nursed by mothers fed the gluten diet weighed less at weaning time than did those of mothers fed the complete diet. Furthermore, the difference between the two groups was maintained from then on, even though all animals were fed the same optimum diet and kept under exactly the same conditions from the time of weaning throughout the rest of their life span.

Figure 5 continues the results until the fifty-sixth week of age; the weight differences between the two groups of animals are still present at the time of writing, more than 20 months after the beginning of the experiment. As mice rarely live much longer than 2 years, it is obvious that the mild nutritional deficiency experienced by the mother during lactation has jeopardized the development of her young for their whole life span.

In the preceding experiment (Figures 4 and 5) the difference between the two groups of NCS mice was certainly caused by the low concentration of lysine and threonine in the diet of the mother during lactation, because the weight-depressing effect could be partly corrected by supplementing the gluten diet with

a proper amount of these two amino acids. Even more interesting, perhaps, is the fact that a profound effect on weaning and adult weight can also be achieved by more subtle nutritional effects exerted on the mother during the lactation period.

Figures 6 and 7 present the results obtained by feeding the nursing mothers a diet (E) containing 15% casein, cyst[e]ine, corn starch, and all known essential growth factors. Diet E is nutritionally adequate, according to usual criteria, since it permits rapid growth of normal adult males or females. When females are fed E diet during lactation, however, the weights of their young are subnormal at weaning time. Moreover, these animals remain abnormally small thereafter, even through transferred permanently to an optimum diet after weaning.

The weight depression caused in the young by feeding E diet to the lactating mother can be prevented by adding 'corn steep liquor'\* to the diet during lactation. As seen in Figure 7, the weaning and adult weights of the young are then as high as those of animals nursed by mothers fed an optimum diet made of mixed natural foodstuffs. Unfortunately, it has not yet been possible to determine the nature of the active substance in the corn steep liquor.

A few attempts have been made to determine whether there exists a period during which the nutritional deficiency of the lactating mother is most critical for the young. As seen in Figure 7, there was still some depression of growth when the E diet was first given to the mother on the fifth day after birth of her young, but there was no significant effect when the beginning of the regimen was delayed beyond that time. The first 5 days of life, therefore, constitute a critical period for the ultimate physical development of the mouse.

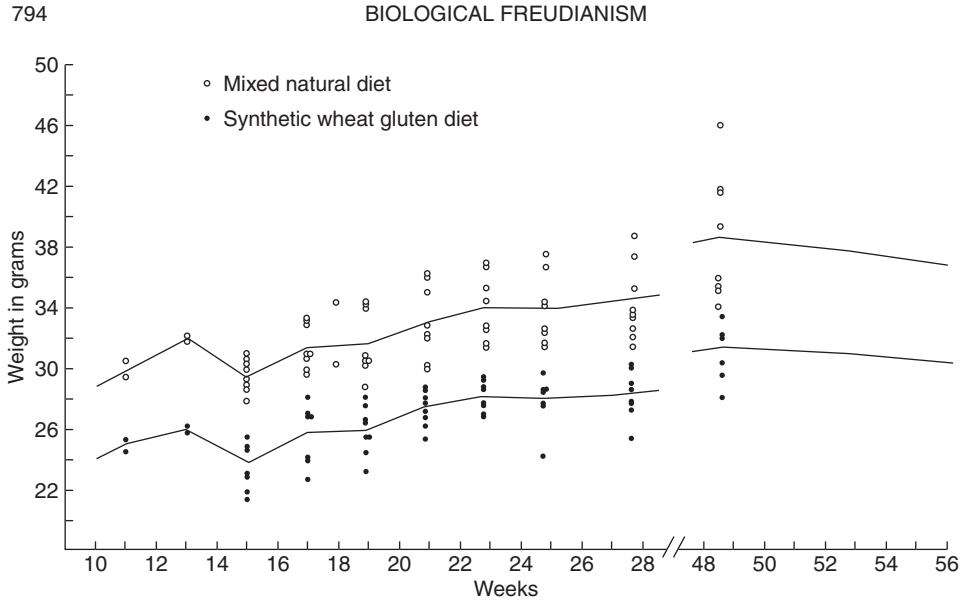
## Early subclinical infections and physical growth

Clinical studies of human children indicate that infectious processes can retard development. The control of childhood infections has probably been one of the factors contributing to the acceleration of growth rates among children in the affluent countries.

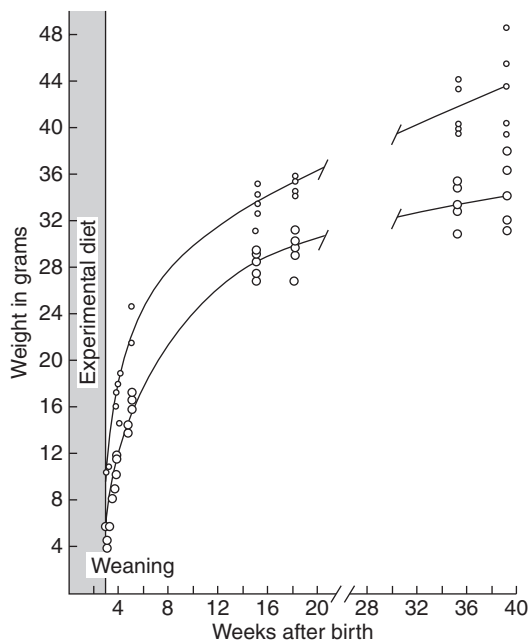
As already mentioned, extensive experience in our laboratory with three mouse colonies derived from the same genetic stock has provided experimental tools for demonstrating the effect of early minor infections on the initial rate and subsequent course of physical development.<sup>5–8</sup>

Table 2 presents the results obtained by contaminating newborn NCS mice a single time two days after birth with intestinal homogenate of adult CFW mice or with material obtained by filtering this homogenate through a millipore filter (porosity 0.47 $\mu$ ). As seen in Table II, the animals thus contaminated weighed less than the controls at weaning time, and they remained smaller thereafter. In contrast, the growth rate was not depressed when the young mice were contaminated with material derived from NCS-D adult animals. This finding is of particular interest since NCS-D animals have been raised

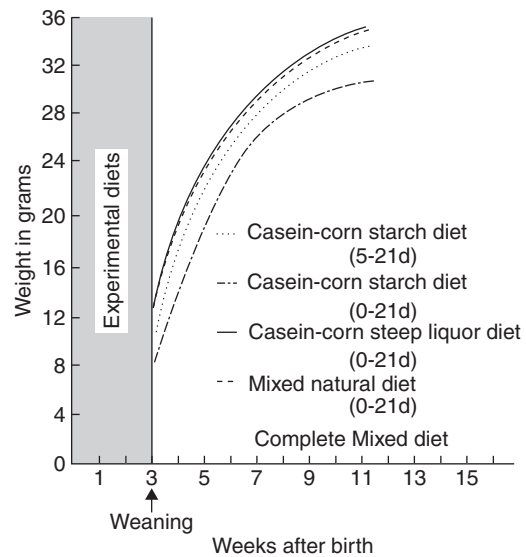
\* The phrase 'corn steep liquor' designates an ill-defined water soluble extract of corn grain, widely used for penicillin production. This material was obtained through the courtesy of Dr. Stanley A. Watson, Corn Products Company, Argo, Illinois.



**Figure 5** Same experiment as Figure 4. On fourteenth week of life, the males were separated from the females and placed in individual stainless steel cages. Note: there is no overlapping between the two groups of males, even though they have been fed the same diet (commercial pellets D & G) since weaning time. The differences between the two groups still persist at the time of writing, 20 months after weaning. The exact parallelism of the two curves expresses the effects of unidentified environmental factors



**Figure 6** NCS-D females fed mixed natural diet (commercial pellets D & G) during gestation, then the following diets from the time of delivery through the lactation period: (1) casein-corn starch diet (E); (2) casein-corn starch diet supplemented with corn steep liquor (ESL). All newborns were fed D & G pellets after weaning (when 21 days old)



**Figure 7** NCS females fed mixed natural diet (commercial pellets D & G) during gestation, then one of the following diets: (1) casein-corn starch diet (E) 5–21 days; (2) casein-corn starch diet (E) 0–21 days; (3) casein-corn steep liquor (ESL) 0–21 days; or (4) mixed natural diet (D & G) 0–21 days. In group given diet E the lactating females were placed on diet 5 days after delivery; in the three other groups, they were placed on the experimental diets from the time of delivery through the lactation period. All newborns were fed D & G pellets after weaning (when 21 days old)

under highly protected conditions in our own laboratories and were essentially free of mouse pathogens.

In many experiments, contamination of newborn NCS mice with CFW intestinal content did not cause any obvious sign of disease other than weight depression; even diarrhea was

unusual. In other cases, however, paralysis of the hind legs was observed and many of the animals so affected eventually died.

The microbial agents of the CFW intestinal content which are responsible for the weight depression of contaminated newborns have not yet been identified; it is probable that two

different kinds of pathogens are involved. One of them, non-bacterial in nature, has been grown *in vitro* in tissue cultures of baby hamster kidney. When newborn NCS mice (2 days old) were contaminated with a tissue culture of this agent, none of them developed paralysis, but all exhibited depression of growth. The depressing effect could be recognized as early as 7 days after infection (Figure 8). The males were separated from the females after weaning (at 3 weeks of age). As seen in

Figure 8, all contaminated males remained smaller than the control males, thereafter; the same was true for the females.

### The multiple effects of early infections

A high level of specific immunity commonly results from infections contracted during early life, or even *in utero*. In fact, the words *premunition*, of infection immunity, were introduced by early immunologists to denote a state of resistance against malaria elicited by acquisition of the plasmodium shortly after birth. More recently, the phrase 'bacterial interference' has been applied to the increase in resistance to staphylococcal infection that can be rapidly established in human babies by contaminating them shortly after birth with a non-virulent strain of this microbial species.<sup>9</sup> It has long been known, of course, that mice infected *in utero* with the lymphocytic choriomeningitis virus continue to harbor the agent thereafter; they are completely resistant to superinfection with this virus, even though their serum does not contain neutralizing antibody for it.<sup>10</sup>

Experiments carried out in our laboratory have brought to light another striking example of antibacterial immunity resulting from intrauterine infection. It was found that while certain colonies of mice are extremely susceptible to pseudotuberculosis caused by *Corynebacterium kutscheri*, other colonies are highly resistant to this organism. As in the case of lymphocytic choriomeningitis, the resistance is related to the fact that all resistant mice are in reality latent carriers of *C. kutscheri*. The latent infection can be activated by administering large amounts of cortisone<sup>11,12</sup> to the resistant animals. Under these conditions, the latent *C. kutscheri* infection becomes active and the cortisone treated animals die of pseudotuberculosis (Tables 3 and 4).

**Table 2** Effect of contamination<sup>a</sup> with intestinal content on growth of NCS<sup>a</sup> mice

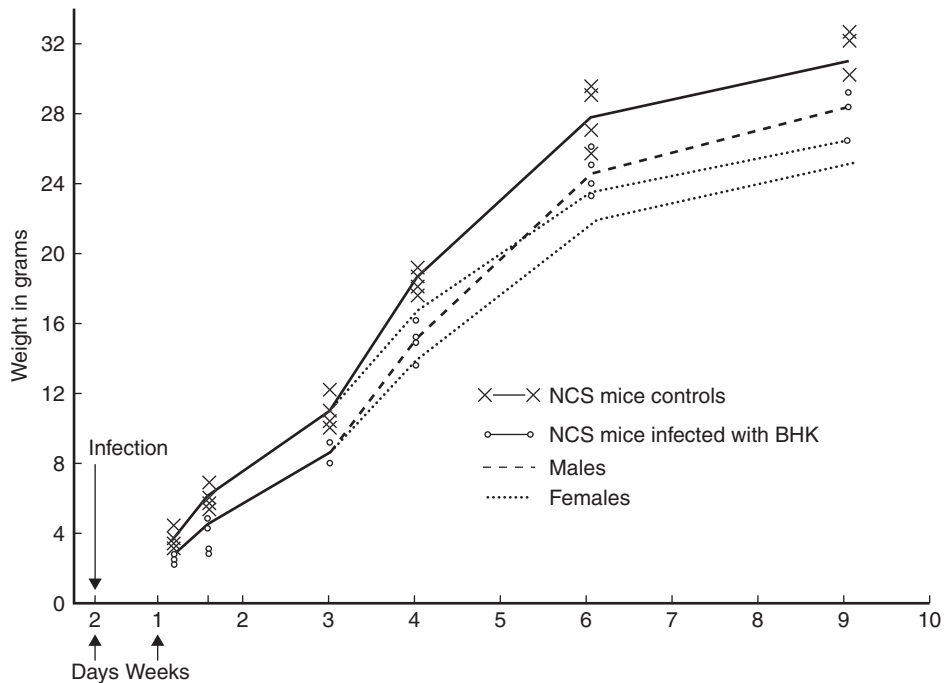
Intestinal Content <sup>b</sup> Derived from	Weight <sup>c</sup> (g) at indicated Age (weeks)						
	2	3	5	7	9	13	17
0 (controls)	9	11	26	31	33	37	39
NCS-D mice	10	12	25	30	33	37	
CFW mice	8	10	16	23	28	32	35
CFW filtrate (diluted)	7	10	17	22			

<sup>a</sup> NCS mice, 2 days old, were contaminated by placing on the lips 1 drop, only once, of material indicated in table. Controls received 1 drop of diluent.

<sup>b</sup> NCS-D mice are maintained in our laboratory and are essentially free of mouse pathogens; they do not harbor *Escherichia coli*. CRW mice were obtained from a commercial breeder. The intestines of adult NCS-D or CFW animals were homogenized in 4 cc of diluent per animal.

<sup>c</sup> Weights are averages for groups of 20–40 animals; rounded to nearest whole number.

The CFW filtrate was obtained by vacuum filtration of CFW homogenate through a Millipore filter (porosity 0.47); the filtrate was diluted a hundredfold before use.



**Figure 8** Weight curves of NCS mice controls, and of NCS mice contaminated 2 days after birth with a tissue culture (baby hamster kidney) of material originally obtained from a bacteria-free filtrate of intestinal contents of adult CFW mice. Males were separated from females on third week. All animals were fed D & G pellets

**Table 3** Susceptibility of mouse strains to *Corynebacterium Kutscheri*

Mouse Strain	Animals Dead of Infection <sup>a</sup>		
	Males	Females	Total %
Albino	50/50	50/50	100
Black	0/50	0/50	0
F <sub>1</sub> (A♀ × B♂)	75/103	50/100	61
F <sub>1</sub> (B♀ × A♂)	68/107	50/88	61

<sup>a</sup> Infection i.v. with  $0.2 \times 10^{-4}$  ml. of culture; deaths occurred within 10 days. (Gross lesions present in surviving F<sub>1</sub> mice; absent in Black mice.)

**Table 4** Activation of *C. Kutscheri* by cortisone (10 mg. subcutaneously)

CC57B1/6 mice housed	Sex	Days of death after cortisone administration
5 per box (sawdust)	Males	6, 7, 14, 14, 14
	Females	14, 14, 14, 17, 17
Isolated (metal cage)	Males	6, 6, 6, 8, 10
	Females	6, 6, 6, 7, 10

Thus, a multiplicity of lasting effects can result from infections acquired during early life, even when the infectious agent is not highly pathogenic. The effects considered in the preceding pages include retardation of development during the lactating period, reduced stature during adulthood, and changes in the immunological state. The immunological effects deserve some further emphasis. While it is obvious that the heightened resistance to superinfection constitutes a lasting advantage, its value to the host is limited by its immunologically specific character. In any case, the advantage is often lost as a result of physiological stress, since, as is well known, many infectious agents become active in the course of such conditions. It is probable, in fact, that most of the endogenous infections that constitute such an important cause of disease in adult life have their primary origin in infections contracted during very early life.

### Nutritional state and resistance to disease

In the experimental models considered so far, the environmental factors acted on the affected organism during the very early periods of its development. Needless to say, the organism continues to respond to the environment and to be thereby modified throughout its life. For example, the quantitative and qualitative aspects of food intake and utilization by the adult animal are directly and rapidly reflected in the level of resistance to disease.

Surprising as it may seem, there is very little precise knowledge concerning the relationship between nutritional state and resistance. In fact, the belief in such relationship has been established more by reiteration than by demonstration. Granted the paucity of knowledge, it is certain, nevertheless, that the younger the animal (or the human being) the more profound and varied are the effects of nutritional deficiency on resistance. Two different models will be mentioned here, each illustrating the effect of a particular type of dietary regimen on the resistance to stress of young adult mice.

We have shown elsewhere, for example that mice still in the growing phase recover from the weight loss caused by bacterial endotoxin only if supplied with large doses of a complete

dietary amino acid mixture. Young animals do not recover from the weight loss caused by endotoxins when their diet is low in lysine and threonine.<sup>13</sup> Bacterial endotoxins apparently increase catabolism and new tissue synthesis is adequate only when the diet has the proper composition.

It has been found also that the ability of young mice to develop immunity to tuberculosis is dependent upon the presence in the diet of unidentified materials that occur in certain natural foodstuffs. This dietary effect has been demonstrated by using as a vaccine either BCG or a small amount (0.02 mg) of mycobacteria killed with ethylene oxide.<sup>14,15</sup>

These results indicate that the nutritional state at the time of first exposure to certain pathogens conditions the character of both the physiological and immunological responses. Thus, nutrition during the early stages of life determines not only the extent of the damage caused by infectious processes but also the subsequent ability of the young organism to overcome the delayed effects of infection.

### The experimental study of sociomedical problems

Needless to say, many types of early influences other than nutrition and infection can exert effects that persist throughout the life span. For example, temperature and humidity, housing conditions, and the degree of crowding, are a few of the many environmental factors that modify lastingly the initial rate of growth, the ultimate size of the adult, resistance to various forms of stress, and, indeed, most physiological as well as mental characteristics. It would be desirable, or course, to understand the precise mechanisms responsible for the profound effects exerted by such environmental forces. Useful working hypotheses could be formulated by considering hormonal activities, anatomical development, cellular metabolism, immunological processes, and other forms of tissue response, including those affecting mental attributes. My purpose, however, was not to discuss mechanisms but rather to illustrate that laboratory models can be devised for the study of the biomedical aspects of social situations.

I have tried to illustrate that the investigator can reproduce in the form of laboratory models most of the social conditions that have brought about the socioepidemiological phenomena mentioned at the beginning of this report, namely the accelerated physiological development of children among Westernized people, the spontaneous changes in the pattern of disease that have occurred during the past century, and the physical and mental retardation of deprived people in certain parts of Central America. The study of such experimental models throws light on obscure sociomedical problems, and should help in the formulation of social programs for their control.

Consider for example one of the human tragedies in the highland villages of Guatemala. During the first few months of their life, the Indian babies develop at a rate compatible with the values of the Iowa standard—at least its lower level. Around the fifth month of life, however, many them become sick and their growth rate falls dramatically. In fact, a very large percentage of them die at that time or shortly after from a great variety of pathological conditions. Pathogenic microorganisms are so ubiquitous in the Guatemalan villages that virologists, bacteriologists, and parasitologists have no difficulty in isolating

several different types of pathogens from the sick babies. There is no doubt, of course, that infection plays a large role in infantile morbidity and mortality. But our experimental models suggest that the nutritional state of the mother during the lactation period might be as important as the presence of pathogens, because it conditions the resistance of her baby to infection.

The laboratory models considered in the present report were devised to investigate some of the health problems of deprived populations. Other types of models would have to be developed for the problems of affluent populations. Still other models can be used to study various types of behavioral disturbances; references 16, 17, and 18 are typical of recent publications in this field.

Whatever the peculiarities of the physical and social environment, many problems of adulthood and old age will be found to be the distant manifestations of environmental factors that were influential during the formative years of life. This relationship is well recognized, of course, with regard to emotional experiences and mental health. It can be demonstrated even more convincingly for early biological experiences and most aspects of physical health. In affluent as well as in deprived populations the most compelling sociomedical problems have their origin in the lasting and often irreversible effects of early environmental influences.

From all points of view, the child is truly the father of the man, and for this reason we need to develop an experimental science that might be called biological Freudianism. Socially and individually the response of human beings to the conditions of the present is always conditioned by the biological remembrance of things past.

## Summary

Many experiences of early life affect the biological characteristics of the adult in a lasting manner. This phenomenon has been illustrated by epidemiological observations in man and by several experimental models in mice.

It has been shown, for example, that when newborn animals are nursed by mothers fed diets that are slightly inadequate, their size remains subnormal throughout their life span, even though the young are fed an optimum diet after weaning. A similar depression of growth can be produced by subclinical infections shortly after birth.

Decrease in resistance to various forms of stress can be brought about in young animals by various types of nutritional and environmental disturbances so mild that their effects are not recognized when the animals are maintained under usual laboratory conditions.

These findings indicate the possibility of devising laboratory models for the analysis of many puzzling sociomedical problems.

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