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DEPRIVATION IN PSYCHOBIOLOGICAL DEVELOPMENT



PAN AMERICAN HEALTH ORGANIZATION
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DEPRIVATION IN PSYCHOBIOLOGICAL DEVELOPMENT

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NOTE

At each meeting of the Pan American Health Organization Advisory Committee on Medical Research, a special one-day session is held on a topic chosen by the Committee as being of particular interest. At the Fourth Meeting, which convened in June 1965 in Washington, D.C., the session focused on deprivation as a factor in psychobiological development. This volume records the papers presented and the accompanying discussions.

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Special Session on
**DEPRIVATION IN
PSYCHOBIOLOGICAL DEVELOPMENT**

Moderator: Dr. H. W. Magoun

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OPENING STATEMENT

Horace W. Magoun, Moderator

The special program adopted for this meeting on Deprivation in Psychobiological Development is a direct outgrowth and, to a degree, an elaboration of aspects of last year's special program, which was devoted to discussion of the environmental determinants of community well-being. It was chaired by Dr. Wolman and keynoted by Dr. Payne. As I recall, Dr. Wolman opened with a quotation from Hippocrates, and when Dr. Payne's turn came he was momentarily at a loss, for he had intended to use the same quotation.

Out of deference to today's speakers, I shall refrain from quoting Hippocrates and so avoid stealing their thunder. Rather, I have selected a text from the English scholar-physician John Locke. In Amsterdam on the last day of the year 1686, Locke finished the fourth and final book of his *Essay Concerning Human Understanding* and, with it, inaugurated contemporary study of the subject of today's program. He had been working on this *Essay* for two years in Holland, having fled Oxford in 1684 on being accused of behaving fractiously toward the English king. Though rumor implicated a Dutch mistress, Locke had chosen Holland both because the climate suited his health better and because, as he wrote, there was but little beer in France.

In the section "Of Ideas" in his *Essay*, Locke said:

Let us then suppose the mind to be, as we say, white paper, void of all characters, without any ideas. How comes it to be furnished? Whence comes it by that vast store which the busy and boundless fancy of man has painted on it with an almost endless variety? To this I answer in one word, from experience. In that all our knowledge is founded. I think it will be granted easily that if a child were kept in a place where he never saw any other but black and white till he were a man, he would have no more ideas of scarlet or green than he that from his childhood never tasted an oyster or a pineapple has of those particular relishes.

A variety of contemporary studies have begun to move a short way through the great door opened by Locke's *Essay* to explore the manner in which brief recurring signals, generated by the environment at peripheral organs of sense, are able to influence the long-time performance of the brain and so contribute to psychobiological development. Two recent clinical presentations impressed me greatly as being relevant to this question. First, the report of the late President Kennedy's Panel on Mental Retardation pointed out that of the large numbers of cases of mental retardation in this country, only 20 per cent were attributable to organic disturbances of the brain—embryonic defects, in-born errors of metabolism, infections, perinatal

injuries, or other trauma. In 80 per cent of the cases, no such organic pathology could be identified; these latter cases, it was proposed, were functional in origin. Because the major proportion of them were found in disadvantaged populations, sociocultural deprivation, a lack of environmental enrichment, and an absence of verbal and cognitive stimulation were all implicated in their etiology. Significantly, subsequent provision of these missing environmental factors seemed to go a long way in remedying the deficit.

Second, a presentation on protein-calorie malnutrition in last year's meeting of this group pointed out that mental retardation was a conspicuous feature of such malnourished children; again, succeeding provision of the missing input, in the form of protein-rich animal or dairy foods, went a long way toward ameliorating the impairment.

These instances implicate two important factors in normal psychobiological development: first, a rich diet of environmental stimulation; second, a viable protein metabolism, presumably of the brain. They even suggest that modification of neuro-protein metabolism may constitute the mechanism by which environmental stimulation promotes psychobiological development; for these clinical presentations were not made in a vacuum, but rather against the background of the great current advances in molecular and cellular biology that have identified, in the mechanisms of genetic biochemistry, the involvement and specification of nucleotide sequences in the DNA of the nucleus of the cell, their transfer to and replication in the RNA of the cytoplasm, and the templates provided by these molecular codes for protein metabolism and enzyme production.

An increasing number of investigators have proposed that nature has not been profligate

enough to have evolved more than a single coding mechanism of this fundamental nature for information storage and retrieval in biology. They suggest that current advances in molecular genetics may be applicable to neural function as well. Their findings imply that afferent stimulation may specify the cytoplasmic RNA of neurons of the central nervous system, in a Lamarckian kind of fashion, and thus modify their subsequent protein metabolism and the enzymes they elaborate as transmitter substances that lead to succeeding patterns of neural firing, so as to induce learning and memory in the brain.

Dr. Dubos and I have enjoyed advising Drs. Allen and Martins da Silva on the organization of today's program on this general field. We think they have assembled a remarkably fine group of contributors to this exciting current investigative area who can tell us about the recent advances.

You will note that the initial part of the program is directed toward basic studies and the latter part to the behavioral, social, and cultural aspects of the findings, in both animal and human populations. We are sorry to learn that Dr. Holmberg will be unable, because of illness, to be present. We have prevailed upon Dr. Thompson, who was to be a discussant, to elaborate some of his own valuable material in the program.

We want to open with molecular and neurochemical studies, then move to neurophysiology and from there to nutritional studies. I feel that all of us are privileged to be able to hear distinguished specialists in each of these areas. I think it is most appropriate that the initial paper will be presented by the contemporary John Locke of Sweden, Holger Hydén, of the University of Göteborg.

GENIC STIMULATION OF NEURONS AND GLIA IN LEARNING WITH SYNTHESIS OF ADENINE-URACIL-RICH RNA *

Holger Hydén

Neurons have a large amount of RNA. In learning experiments, a production of RNA and base-ratio changes have been shown to occur in neurons and glia (Hydén and Egyhazi, 1962, 1963, 1964). Physiological and chemical stimulation, on the other hand, were found to give an increase of RNA in neurons and a decrease of RNA in glia (Hydén and Pigon, 1960; Egyhazi and Hydén, 1961).

In the present paper the following problems will be discussed, using earlier and new data on RNA obtained from the nervous system.

1. Does the biochemical response of neurons and glia in learning differ from the response after physiological or chemical stimulation? Does the RNA composition reflect nuclear and genic activity when an animal is faced with a situation not encountered before?

2. What may be the mechanism behind inverse RNA changes between glia and neurons? In this connection I shall take up the question whether a transfer of RNA may occur between glia and neurons, in contradistinction to what happened in learning, where the RNA changes went in the same direction in both neurons and glia.

3. Furthermore, a genetic aspect will be discussed on the basis of RNA data, demonstrating that in brain cells also factors in the environment may lead to a genic stimulation and release of genome activities. A biochemical glia error in a neurological disease may serve to demonstrate a case in which such a genic activity is undesirable and functionally harmful.

* The studies reported on here have been supported by the United States Air Force under Grant No. EOAR 63-28 through the European Office, Office of Aerospace Research; The National Multiple Sclerosis Society, New York; and The Swedish Medical Research Council.

Methods of analysis

All data referred to in what follows have been obtained with microchemical technique on isolated neurons or samples of glia (Edström, 1958 *a* and *b*, 1960 *a* and *b*, 1964; Hydén, 1959). The reason is the complicated structure of the brain and the intimate structural relationship between glia and neurons.† Inverse biochemical changes occur in neurons and the surrounding glia. Therefore, even if one γ of material is taken from the brain, the sample will probably consist of 50 per cent nerve-cell material and 50 per cent glia. Inverse biochemical changes in these two types of cells will most certainly be leveled out in a bulk analysis. Differentiated biochemical response may also escape detection if γ -amounts of brain material are subjected to analysis. Therefore, nerve cells, including the first part of the dendrites, and neuronal glia have been isolated from precipitated or fresh brain material. A de Fonbrune micromanipulator and freehand dissection (of the fresh material) have been used. In some cases only nerve-cell nuclei were used for RNA analysis. For each analysis 25 to 30 nuclei were isolated by microdissection. The technique is briefly as follows: The isolated nerve cells, placed on a glass slide, were treated with cold phenol-saturated water for fifteen minutes, followed by cold absolute ethanol for ten minutes, and then covered with paraffin oil. This treatment causes the nuclei to contract slightly, which is hardly noticeable at a magnification of 600 \times . The nucleus from

† The two types of cells composing the central nervous system consist of nerve cells with their processes, dendrites and axon, and different types of glial cells. The thin, delicately folded, membrane-like processes of the glia intertwine and ensheath the neurons except at places where the synaptic knobs take up part of the neuronal surface.

each nerve cell could then be easily removed with the aid of the micromanipulator. Twenty-five nuclei were used for each RNA analysis. It was carefully checked that the phenol treatment precipitates all RNA in nerve cells. For the quantitative and qualitative analysis of RNA, the micromethods developed at this laboratory were used. A detailed technical paper describing the micro-electrophoretic procedure has recently been published (Edström, 1964). For each analysis 500 to 700 $\mu\mu\text{g}$ of RNA were used. The random error in the determination of the RNA in single nerve cells was found to be 4 per cent. The average coefficient of variation of the micro-electrophoresis of the analytical results was 5 per cent for nerve-cell RNA and 7 per cent for yeast RNA. In one case it was possible to compare the result of the micro-electrophoretic separation of hydrolyzed RNA from biological material with that obtained by conventional macrochemical electrophoretic separations. The analysis of nucleolar and ribosomal RNA of mature starfish oocytes gave the same results with both methods (Edström, Grampp, and Schorr, 1961). In model experiments on purified samples of RNA, the correspondence between macro- and micro-electrophoresis is clear (Edström, 1964).

The advantage of micro-electrophoresis over macro-electrophoresis is the possibility of analyzing samples at the cellular level. This has proved to be a *sine qua non* for nerve tissue since its two cellular components, neurons and glia, differ in amount and composition of RNA.

The neuronal and glial RNA were determined on the same dry-weight basis, determined by quantitative X-ray microspectrography (Brattgård and Hydén, 1952) and using a scanning and computing densitometer (Hydén and Larsson, 1956 and 1960).

Response of neurons and glia to stimulation and to learning

Base ratios of RNA upon physiological stimulation

To stimulate the neural function, rotatory horizontal and vertical vestibular stimulation

through 120° , changing direction every two seconds, was used. It was found that the so-called Deiters' nerve cells in the vestibular nucleus of the brain stem and nerve cells from the reticular formation increased their RNA content by 5 to 25 per cent. (Deiters' nerve cells, rat, from 680 to 740 $\mu\mu\text{g}$ [horizontal], from 680 to 850 $\mu\mu\text{g}$ [vertical rotation]; nerve cells of nucleus gigante-cellularis, rat, from 540 to 590 $\mu\mu\text{g}$.) (Hydén and Pignon 1960, Hydén and Egyhazi, 1963.) But no significant change in the RNA base ratios could be observed in any of these experiments. The composition remained that typical for the cytoplasmic, high-polymer ribosomal RNA, which for Deiters' nerve cells, rat, is A 20.5 G 33.7 C 27.4 U 18.4.

The nuclei of nerve cells are usually small in comparison to the bulk of the cytoplasm. In Deiters' nerve cells from rats, for example, they contain 30 $\mu\mu\text{g}$ of RNA compared to the 650 $\mu\mu\text{g}$ of cytoplasmic RNA. This nuclear RNA has the following base ratios: A 21.4 G 26.2 C 31.9 U 20.5 (Hydén and Egyhazi, 1962). The explanation is presumably that the nuclear ribosomes and the nucleolar RNA, which is of ribosomal RNA type, dominate.

This means that upon physiological stimulation the newly formed RNA of the nerve cell had the same base composition as the original RNA, being of the ribosomal RNA type.

Base ratios of RNA upon chemical induction of RNA synthesis in neurons

Tricyano-amino propene (triap) administered to animals at 20 mg per kg has been found to cause an increase *within one hour* in the amount of RNA per nerve cell, the respiratory enzyme activities, and total dry weight including proteins. The base ratios of the total nerve-cell RNA were found to change significantly (Egyhazi and Hydén, 1961).

The quantitative increase was 570 $\mu\mu\text{g}$ of RNA in addition to the original amount of 1550 $\mu\mu\text{g}$ per nerve cell. Table 1 shows the RNA base ratios of the control nerve cells. The effect of the chemical agent was to change significantly the values of guanine and cytosine.

TABLE 1. Microelectrophoretic Analyses of Composition of RNA in Deiters' Nerve Cells of Rabbits Treated with 20 mg/kg of Tricyano-amino Propene and Killed 1 Hour Later (Purine and Pyrimidine Bases in Molar Proportions in Percentages of Sum). Total Amount of RNA Increased Significantly from 1550 (± 78) μg /cell to 2120 (± 106) μg /cell

	CONTROLS	TRIAP	Δ RNA FRACTION
Guanine	19.7 \pm 0.37	20.5 \pm 0.31	22.5 \pm 1.61
Adenine	33.5 \pm 0.39	34.6 \pm 0.28	37.7 \pm 1.66
Cytosine	28.8 \pm 0.36	26.7 \pm 0.24	21.0 \pm 2.03
Uracil	18.0 \pm 0.18	18.2 \pm 0.20	18.8 \pm 0.91
$\frac{G + C}{A + U}$	1.65 \pm 0.023	1.58 \pm 0.018	1.42 \pm 0.090
$\frac{A}{U}$	1.09 \pm 0.021	1.13 \pm 0.021	1.20 \pm 0.103
No. animals:	5	11	
No. cells:	490	1200	

(From Egyhazi and Hydén, 1961)

A more informative insight into the changes occurring in the RNA composition is obtained if the base-ratio alterations are referred to the *change* in the amount of RNA (called here the Δ RNA fraction or Δ RNA) and not to the final amount. This means, for instance, in the case of an increase of the RNA content with a simultaneous change in the base ratios (as in the case above after injection of tricyano-amino propene), that the chemical change of RNA is described as a synthesis of a newly formed amount of RNA (Δ RNA) with a different base-ratio composition from that of the original RNA. Similarly, a decrease in the amount of RNA with a simultaneous change in base-ratio composition can be considered a loss of an RNA fraction (Δ RNA) in such a way that the composition of the Δ RNA removed differs from that of the original RNA.

Table 1 shows that the increase of the guanine and decrease of the cytosine value is characteristic for the final RNA. This is more accentuated if the changes are computed on the newly formed Δ RNA fraction, as described above. In both cases (final RNA and Δ RNA) the ratio $\frac{G + C}{A + U}$ does not differ from 1.7 in the control nerve cell, being 1.6 and 1.4 respectively. This means that the newly synthesized RNA is of the ribosomal type.

As was pointed out above, the amount of RNA in the nucleus of these big nerve cells is

only a fraction of the RNA total, 55 μg of 1550 μg , or 3.5 per cent. Considering, however, the importance of the nucleus for protein synthesis in the cell, the nuclear RNA composition was analyzed in control nerve cells and in the cells after induction of RNA synthesis by triap. This was done by removing the nucleus from each cell by microdissection and pooling the RNA collected from 25 nuclei for each electrophoretic analysis.

Table 2 demonstrates the findings. An average loss of 16 per cent of RNA from the nucleus had occurred. If this loss (Δ RNA, column 4) is considered to represent an RNA constituent of the nucleus, it has an unusually high amount of cytosine and uracil. The ratio $\frac{G + C}{A + U}$ is 0.73, compared to 1.34 for the control nuclear RNA and 1.52 for the total nuclear RNA of the triap nerve cells.

Thus, the nuclear RNA composition after treatment with triap is of a more ribosomal character, since the guanine-cytosine values are increased. This fact may be explained as a consequence of the activity of the nucleus during the high RNA synthesis in the cytoplasm. Therefore, the question might be raised whether the base ratios of the lost RNA

TABLE 2. Microelectrophoretic Analyses of Composition of Nuclear RNA in Deiters' Nerve Cells of Rabbits Treated with 20 mg/kg of Tricyano-amino Propene and Killed 1 Hour Later (Purine and Pyrimidine Bases in Molar Proportions in Percentages of Sum). Total Amount of RNA Decreased Significantly from 56 (± 2.7) $\mu\mu\text{g}/\text{nucleus}$ to 47 (± 1.9) $\mu\mu\text{g}/\text{nucleus}$

	CONTROLS	TRI-A-P	Δ RNA FRACTION
Adenine	21.3 \pm 0.42	21.5 \pm 0.54	20.3 \pm 3.75
Guanine	26.6 \pm 0.27	30.0 \pm 0.45	9.4 \pm 7.10
Cytosine	30.8 \pm 0.38	30.4 \pm 0.49	32.8 \pm 3.56
Uracil	21.3 \pm 0.43	18.1 \pm 0.44	37.5 \pm 7.36
$\frac{G + C}{A + U}$	1.34 \pm 0.022	1.52 \pm 0.040	0.73 \pm 0.172
$\frac{A}{U}$	1.00 \pm 0.028	1.19 \pm 0.041	0.54 \pm 0.148
No. animals:	22	26	
No. nuclei:	275	380	

(From Hydén and Egyhazi, 1962)

(A 20.3 G 9.4 C 32.8 U 37.5) represented a "messenger" RNA. Furthermore, since the nucleolus is the main site of the ribosomal RNA synthesis in the nucleus and has an RNA of ribosomal type, the finding of a more ribosomal character in the nuclei is not surprising.

In using phenylcyclopropylamine, a powerful inhibitor of monoaminoxidase, 0.3 mg/kg body weight, an increase in neuronal RNA of 30 per cent per neuron was obtained in one hour and a decrease in glial RNA of almost 50 per cent (Hydén and Egyhazi, to be published). Significant base-ratio changes involving guanine and cytosine were found. Moreover, the cytochrome oxidase activity increased in the neurons by 250 per cent and decreased in the glia by 30 per cent. We also used actinomycin D, given intravenously to rabbits in doses of 0.3 mg three to seven hours before the injection of phenylcyclopropylamine. We found that the actinomycin not only inhibited the RNA changes but also produced an RNA loss of 100 $\mu\mu\text{g}/\text{cell}$. The base composition of this lost RNA fraction was A 25.7 G 43.3 C 23.0 U 8.0. The conclusion from these experiments was that the RNA production induced by the chemical is immediately DNA-dependent.

Furthermore, it is interesting that through the influence of actinomycin there was actually a loss of RNA, the base composition of which was highly asymmetric.

In considering the newly synthesized cytoplasmic RNA after both physiological stimula-

tion and induction by a chemical agent, it can thus be said that this RNA has the base ratios of a ribosomal RNA.

The emergence of adenine-uracil-rich RNA during learning experiments

Two types of learning experiments were performed on rats. Cortex and brain-stem neurons involved in the learned behavior were analyzed. In contrast to the results after physiological and chemical stimulation, the RNA formed in the neurons during learning had high adenine-uracil values in one case and was asymmetric and had high adenine values in the other.

The adenine-uracil-rich RNA fraction found has a low $\frac{G + C}{A + U}$ ratio of 0.70 to 0.90. It could not be extracted by cold perchloric acid, acetic acid, or water. The same was the case with the asymmetric, adenine-rich RNA. It is therefore likely that this fraction consists of polymer RNA and not of small molecules.

In mammalian cells, nuclear and cytoplasmic RNA fractions have been described that stimulated the incorporation of amino acids. They furthermore had a low $\frac{G + C}{A + U}$ ratio of 0.9—1.0 and an asymmetric base-ratio composition with adenine values higher than the uracil values (Brawerman, Gold, and Eisenstadt, 1963; Moyer, McCarthy, and Bolton,

1963). The question of protein synthesis in mammalian cells and its dependence on messenger RNA with a slow turnover or on rapidly synthesized RNA in the nucleus or cytoplasm is, however, far from settled.

In the case of the data presented here, work now in progress will elucidate possible template activity and other characteristics of the different RNA functions of neurons and glia.

In the first experiment, right-handed rats were induced to use the left hand in retrieving food from far down a narrow glass tube (Hydén and Egyhazi, 1964). Training periods of 2×25 minutes per day were given. The neurons of both sides of the cortex, and from those areas whose destruction prohibited transfer of handedness, were analyzed. These neurons have a large nucleus compared to the cytoplasm. Therefore, the analytical result will mainly reflect nuclear RNA. Eighty-eight rats were used for the analysis of 14,000 cortical neurons. The advantage with this learning experiment is that the controls are present in the same brain. Therefore, a paired *t*-analysis could be per-

formed on the results from the neurons of both sides. Other control experiments were also performed.

A significant increase in the amount of RNA per cell from the learning side of the cortex occurred. In an extension of the published work, the amount of RNA was found to have increased from 220 $\mu\mu\text{g}$ of RNA per 10 nerve cells to 310 $\mu\mu\text{g}$.

When the base ratios of the neuronal RNA of the control side were compared with that of the learning side, the ratio $\frac{G+C}{A+U}$ was found to have decreased significantly from 1.72 to 1.51.

In the present paper a detailed analysis has been performed to investigate whether the extent and type of RNA change could be correlated to the learning process in the individual case. In Table 3, therefore, the data are divided in two groups. The cell material from the cortex of animals 1 and 2 was taken on the rising part of the learning curve on the third

TABLE 3. Characteristics of RNA Formed per Neuron During Transfer of Handedness, Correlated to Training Periods and Performance of Animals

ANIMAL	DAYS OF TRAINING (2×25 min/day)	NUMBER OF SUCCESSFUL REACHES	RELATIVE INCREASE OF TOTAL RNA PER NEURON (per cent)	Δ RNA COMPOSITION
1	3	107	33	A 25.5 G 36.1 C 9.7 U 28.7
2	5	163	23	A 24.5 G 35.7 C 11.7 U 28.1
3	8	625	63	A 26.2 G 34.9 C 16.1 U 22.8
4	9	1041	105	A 21.0 G 35.2 C 24.0 U 19.8

to the fifth day—that is, during an early part of the learning period. The material from the other two rats was taken on the asymptotic part of the curve on the ninth to the tenth day. In this case the animals had already reached the maximal number of successful performances per training period on the sixth to seventh day.

The increase in RNA content per neuron of the three-to-five-day animals lies at 25-30 per cent. Qualitatively, the RNA formed in the neurons—the Δ RNA—is characterized by a DNA-like base-ratio composition with adenine and uracil values around 26. (Rat DNA has the following base composition: A 28.6 G 21.4 C 20.4 U 28.4.) The cytosine values were remarkably low. The results were statistically significant.

This result is no longer obtained from the animals that had trained for nine to ten days and performed with a maximal number of reaches and movements—seventy to eighty reaches per period of twenty-five minutes. The RNA result deviated both quantitatively and qualitatively from those of Group One. The relative RNA increase per neuron in the learning cortex was 60 to 100 per cent. The base-ratio composition of the RNA formed (Δ RNA) is similar to that of ribosomal RNA, especially in the case of animal number 4.

While the relative RNA increase per neuron was small during the early and acute part of the learning process, the nuclear RNA formed had a DNA-like base-ratio composition. Thus, a stimulation of the genome seems to occur early in a learning situation the animal has not encountered before. By contrast, when the animals performed well according to criterion, this RNA with high adenine-uracil values was replaced by an RNA with a ribosomal base composition. At this stage of the learning, the relative increase of Δ RNA was greater than during the first stage. Thus, a differentiated formation of RNA occurs during a learning period in the neurons engaged, and the beginning seems to be characterized by a genic stimulation, to judge by the character of the RNA formed.

In the second learning experiment young rats had to learn how to balance on a thin, one-meter-long steel wire strung at a 45-degree angle between the floor and a small platform with food on it (Hydén and Egyhazi, 1962 and 1963). They were trained for periods of 45 minutes a day. Seventy-eight rats were used for the analysis of 12,000 nerve cells. *Vestibular Deiter's nerve cells* clearly involved in this balance experiment were analyzed. The cytoplasm of these nerve cells is large in comparison to the nucleus. If a whole cell is analyzed, the characteristics of nuclear RNA will therefore drown in the bulk of the cytoplasmic RNA, since the ratio of nuclear to cytoplasmic RNA is 1:50. No base-ratio changes were detected during learning in the cytoplasmic RNA, although an increase from 680 to 750 $\mu\mu\text{g}$ of RNA was determined. Consequently, the nuclei were isolated and the base ratios of the nuclear RNA investigated. Then a clear increase in the ratio A/U of the nuclear RNA was found (1.06 to 1.32), but no significant change in the ratio $\frac{G + C}{A + U}$.

Since no control neurons can be obtained from the same brain in such an experiment, four different types of control experiments were performed, with physiological stimulation and stress involving the vestibular pathways. No significant changes in the A/U ratio were found in these controls, although a significant increase in RNA per neuron could be determined. This signifies that the increase in adenine and decrease of uracil occurring was *specific* for the learning experiment. What may be the significance of the synthesis of such a nuclear RNA fraction, with such high adenine values?

In defined parts of chromosomes from *Chironomus*, RNA has been extracted and found to have an asymmetric composition with high adenine values (Edström and Beer mann, 1962). This type of nuclear RNA stimulating amino acid incorporation has been found in *Euglena* (Brawerman, 1963), and also in starfish oocytes (Edström, 1961).

The conclusion is, therefore, that the nuclear RNA with high A/U ratio found in the second type of learning experiment in rats was chromosomal RNA.

Table 4 presents earlier and new data obtained on both nerve-cell nuclei and glia in this learning experiment. The increase in the total amount of nuclear RNA of the neurons was estimated at around 20 per cent, as was also the increase of glial RNA. The Δ RNA fraction of the nerve-cell nuclei is seen to have a very high adenine and a low uracil content.

It may be noted that the ratio $\frac{G+C}{A+U}$ of 1.25 does not differ significantly from the corresponding control value of 1.38. The enormous increase in the A/U ratio, from 1.06 to 5.9, is, however, striking.

It should be observed, however, that this A/U value of 5.9 contains a great error owing to the two errors in U in control and learning. But since there is a significant change in A/U between control and learning—1.06 and 1.32, respectively—and a significant increase and decrease of adenine and uracil, respectively, in the Δ RNA fraction, the A/U value of Δ RNA must be high. In order to obtain a more reliable value of this latter A/U value a greater number of measurements would have been needed.

These are not available at present, since the data used in this case were not originally prepared for an analysis of the Δ RNA fraction.

This may be compared to the A/U ratio of the RNA produced in the Balbiani rings in chromosomes of *Chironomus*, which was found to be around 2 (Edström and Beermann, 1962). Since control experiments to the rat learning experiments demonstrated the significance of the increased adenine and decreased uracil values of the newly formed Δ RNA in the nucleus, it seems justifiable to assume that this RNA is of chromosomal origin.

As Table 4 shows, the neuronal glia reacted in the following way during learning: The adenine content of the Δ RNA fraction increased by 70 per cent, and the cytosine content is markedly decreased in comparison to the controls. The glial Δ RNA is very similar to the adenine-rich, asymmetric RNA being formed in the neurons during learning and has a $\frac{G+C}{A+U}$ ratio of 0.7. The high A/U glial ratio of 2.70 indicates that the Δ RNA being formed in the glia during learning is of chromosomal origin in analogy to the Δ RNA formed in the neuron.

TABLE 4. Microelectrophoretic Analyses of Composition of Nuclear RNA in Neurons and Glial RNA of Deiters' Nucleus in a Learning Experiment in Rats (Purine and Pyrimidine Bases in Molar Proportions in Percentages of Sum)

	NUCLEUS			GLIA		
	CONTROL	LEARNING	Δ RNA FRACTION	CONTROL	LEARNING	Δ RNA FRACTION
Adenine	21.4 \pm 0.44	24.1 \pm 0.39	38.1 \pm 3.25	25.3 \pm 0.16	28.3 \pm 0.45	43.0 \pm 2.83
Guanine	26.2 \pm 0.45	26.7 \pm 0.87	28.8 \pm 5.75	29.0 \pm 0.24	28.8 \pm 0.31	27.0 \pm 2.24
Cytosine	31.9 \pm 0.77	31.0 \pm 0.96	26.7 \pm 6.95	26.5 \pm 0.43	24.3 \pm 0.36	14.0 \pm 3.12
Uracil	20.5 \pm 1.01	18.2 \pm 1.11	6.4 \pm 8.08	19.2 \pm 0.27	18.6 \pm 0.21	16.0 \pm 1.88
$\frac{G+C}{A+U}$	1.38 \pm 0.042	1.37 \pm 0.049	1.25 \pm 0.218	1.25 \pm 0.030	1.13 \pm 0.028	0.69 \pm 0.076
$\frac{A}{U}$	1.06 \pm 0.056	1.32 \pm 0.084	5.9 \pm 7.5	1.32 \pm 0.020	1.52 \pm 0.030	2.70 \pm 0.364
No. animals:	5	8		5	6	
No. cells:	500	900				
(From Hydén and Egyhazi, 1962 and 1963)						
No. glia samples:				33	42	

A conclusion is therefore that factors in the environment (that is, the new learning situation not encountered before by the animal) produce stimulation of the genome of the glia and the neurons engaged and that this response can be characterized in biochemical terms.

Analysis of the RNA response in two learning situations has thus shown that neurons and glia engaged in the behavior to be established differ from the response in physiological and chemical stimulation with respect to two important parameters. First, the content of RNA increases in both neurons and glia during learning. In physiological and chemical stimulation, the RNA changes were inverse. Second, adenine-uracil-rich, asymmetric RNA is formed in both glia and neurons during learning. In the cases of stimulation, the RNA being formed had ribosomal RNA characteristics with respect to base ratios.

By inference, the adenine-uracil-rich asymmetric RNA formed in learning is assumed to be of chromosomal type.

Is there a transfer of RNA between glia and their neurons?

The discussion of the results presented above led to the conclusion that during physiological and chemical stimulation RNA of a ribosomal character is formed both in glia and in neurons. In the two types of learning experiments, on the other hand, the RNA synthesized during the course of the learning was of an asymmetric adenine-rich type, probably a chromosomal RNA, to judge by the base-ratio composition.

This finding leads to the problem of the relationship between the neuron and its surrounding glia at a molecular level. It is well established that the morphological relationship between them is a most intimate one. Glial membranes can even invaginate the nerve-cell cytoplasm (Hess, 1958). Furthermore, all parts of the neuronal surface not covered by synapses are covered by glial membranes. From a biochemical point of view, kinetic observations of enzyme activities (Hydén and Lange, 1960 and 1962; Hamberger and Hydén, 1963; Ham-

berger, 1963) have led to the conclusion that the neuron and its glia are coupled energetically and that they form a functional unit of the central nervous system.

Following physiological and chemical stimulation, the RNA and protein content and the respiratory enzyme activities were found to *increase* significantly in the neuron but to *decrease* in the glia. A study of the kinetics of enzyme reactions demonstrated that the neuron is the demanding and dominating partner of the functional unit (Hydén and Lange, 1962). At increased function it rapidly doubled the rate of oxygen consumption. The glia did not change in this respect but resorted partly to anaerobic glycolysis to cover their energy demands. It was but a short step from these measurements to supposing the existence of a mechanism transferring macromolecules between the glia and the neuron. Speculations on a transfer of RNA between neurons or between glia and neurons have been published recently (Roberts, 1964; Schmitt, 1964; Landauer, 1964). In what follows, the discussion of such a mechanism will be based on the data obtained in induced RNA synthesis.

I have chosen the results obtained on vestibular nerve and glial cells after the administration of triap to rabbits (Egyhazi and Hydén, 1961; Hydén and Egyhazi, 1962). The animals were killed one hour after the intravenous injection of 20 mg triap per kg body weight. Quantitatively, an increase of 570 $\mu\mu\text{g}$ of RNA to the existing 1500 $\mu\mu\text{g}$ per nerve cell, and a decrease of 55 $\mu\mu\text{g}$ per glial sample from the control value of 123 $\mu\mu\text{g}$, were found. These are dramatic changes and from a quantitative point of view sufficiently large to serve as a basis for such a discussion.

It was concluded above that the Δ RNA fraction synthesized was ribosomal in character. Table 5 lists the data from both the glia and the neurons, including the calculated composition of the corresponding Δ RNA fractions.

First, it can be noted that the Δ RNA fractions of the neurons and the glia are of the same ribosomal type.

Second, the amount of glial RNA is around one tenth of that per nerve cell determined on the basis of the same volume and dry weight. The amount of Δ RNA fraction determined in the glia is also around one tenth that of the neuronal Δ RNA fraction. The volume relationship of glia to neurons within the lateral vestibular nucleus is not known with certainty, but the following may be said: The big Deiters' cells used in our studies are situated some hundred microns apart. We are concerned with the so-called neuronal glia enclosing the perikaryon of each nerve cell. Taking the figures calculated by Sholl (1960) and Schadé, van Backer, and Colon (1964) on the size of the territories of individual nerve cells, a volume of $10^6 \mu^3$ for the neuronal glia belonging to each Deiters' nerve cell seems reasonable. On the basis of this figure and a volume of around $10^5 \mu^3$ for each nerve cell, this would mean that the volume ratio of nerve cell to glia is 1 to 10. It is not unreasonable, therefore, to assume that the loss of $55 \times 10 \mu\mu\text{g}$ of glial RNA corresponds to the determined increase of $570 \mu\mu\text{g}$ of RNA in

each neuron. These experimentally found values could reflect a transfer of RNA from glia to neurons.

Third, a support for this assumption is supplied by the calculated base composition of the glial and neuronal Δ RNA fractions (Table 5). The values are identical. However, experiments using labeled RNA, which at the present time are impossible to carry out, will be decisive in proving a transfer of RNA from glia to neurons.

A concluding remark may be made at this point with respect to the difference in response of neurons and glia in learning and during stimulation. As has been said, the RNA content increased in both glia and neurons during learning; during stimulation, on the other hand, it increased in the neurons but decreased in the glia. One comment is that the possible mechanism of RNA transfer between glia and neurons expressed in inverse RNA changes is linked to and regulated by the level of neural function. In learning, on the other hand, the establishment of the new functional response releases genomic activities. These express them-

TABLE 5. Microelectrophoretic Analyses of Composition of RNA in Nerve Cells and in Glia of Deiters' Nucleus of Rabbits Treated with 20 mg/kg of Tricyano-amino Propene and Killed 1 Hour Later (Purine and Pyrimidine Bases in Molar Proportions in Percentages of Sum). Total Amount of Nerve-Cell RNA Increased Significantly from 1550 (± 78) $\mu\mu\text{g}/\text{cell}$ to 2120 (± 106) $\mu\mu\text{g}/\text{cell}$; Total Amount of Glial RNA Decreased Significantly from 123 (± 6.2) $\mu\mu\text{g}/\text{sample}$ to 68 (± 3.4) $\mu\mu\text{g}/\text{sample}$

	NEURON		GLIA		NEURON:	GLIA:
	CONTROL	TRIAP	CONTROL	TRIAP	Δ RNA FRACTION	Δ RNA FRACTION
Adenine	19.7 \pm 0.37	20.5 \pm 0.31	20.8 \pm 0.28	20.1 \pm 0.74	22.5 \pm 1.61	21.6 \pm 1.11
Guanine	33.5 \pm 0.39	34.6 \pm 0.28	28.8 \pm 0.64	21.9 \pm 2.15	37.7 \pm 1.66	37.8 \pm 3.19
Cytosine	28.8 \pm 0.36	26.7 \pm 0.24	31.8 \pm 0.27	38.6 \pm 2.40	21.0 \pm 2.03	23.0 \pm 3.33
Uracil	18.0 \pm 0.18	18.2 \pm 0.20	18.6 \pm 0.55	19.4 \pm 0.65	18.8 \pm 0.91	17.6 \pm 1.49
$\frac{G+C}{A+U}$	1.65 \pm 0.023	1.58 \pm 0.018	1.54 \pm 0.030	1.53 \pm 0.090	1.42 \pm 0.090	1.55 \pm 0.138
$\frac{A}{U}$	1.09 \pm 0.021	1.13 \pm 0.021	1.12 \pm 0.058	1.04 \pm 0.051	1.20 \pm 0.103	1.23 \pm 0.122
No. animals:	18	20	9	12		
No. cells:	720	800				
No. glia samples:			50	62		

(From Egyhazi and Hydén, 1961; Hydén and Egyhazi, 1962)

selves in their primary RNA products formed in both neurons and glia.

The synthesis of an asymmetric, adenine-rich RNA in Parkinson's disease

In biopsy material from globus pallidus of patients suffering from Parkinson's disease, the big nerve cells and the surrounding glia were analyzed with respect to RNA (Gomirato and Hydén, 1963).

At a very early stage of the disease, the presence of a highly aberrant RNA was found in the glia. The adenine value was highly increased and those of guanine and uracil decreased, and these changes persisted. The neuronal RNA was less changed. Later during the development of the disease, and from the time the overt clinical symptoms emerged and progressed, similar but not identical changes were characteristic also for the neuronal RNA. The amount of RNA per nerve cell and glial samples was significantly increased, averaging 145 $\mu\mu\text{g}$ RNA/nerve cell (control 116) and 34 $\mu\mu\text{g}$ RNA/glial sample (control 17). These striking base-ratio changes and quantitative RNA changes were found in the biopsies whether the patient had been ill for one year or twenty. Due regard was paid to the time relationship between clinical symptoms and biochemical changes in the neurons and glia in the two sides of the same brain. The conclusion of these analyses was that a biochemical error arises in the glia at a very early stage of Parkinson's disease and involves the synthesis of polynucleotides. The nerve-cell RNA changes were probably secondary to their nature.

Let us discuss the characteristics of the RNA changes occurring in the glia during the course of the disease. In Table 6 the observed base ratios of the controls and the biopsies are seen in the second and third columns. The change in the base ratios is calculated on the increased amount of RNA (ΔRNA , column 4). Clearly an RNA of a highly asymmetric type has been formed in the glia. Especially striking is the unusually high increase in adenine. The ratio

$\frac{G + C}{A + U}$ is 0.79, compared with 1.69 for the control glia. The A/U ratio is 3.18, compared to 1.05 for the control glia RNA.

In the neurons of globus pallidus, the RNA base-ratio changes are less striking (Table 7). The composition of the total RNA shows a significant increase of adenine and decrease of guanine. If the change in composition is referred to the increased amount of RNA (ΔRNA , column 4), in analogy to the treatment of the glia data above, this neuronal RNA is characterized by a decreased $\frac{G + C}{A + U}$ ratio and a high adenine value, as was also the case with the glial RNA. The neuronal changes are less conspicuous, however.

All data indicate the glia as being the type of brain cell in which, in Parkinson's disease, the change in RNA formation begins and is most pronounced. An explanation for this may be the fact that the glia has less RNA content relative to that of the neuron. Therefore, a change in the *nuclear* RNA formation is more easily traced in the glia. To judge by the base ratios and the high adenine content, the Parkinson RNA resembles chromosomal RNA of the type that has been found in *Chironomus* and in starfish.

It may be that Parkinson's disease represents a type of disorder in which factors in the environment (infections, for example) at a crucial period of the life cycle initiate the release of undesirable genomic activities that will lead to the biochemical error in the glia. A more hazardous explanation, for which there is at present no evidence, would be that the ΔRNA fraction reflected a virus infection.

Summary

RNA changes may occur in neurons and glia when the functional equilibrium is changed. On the basis of quantitative RNA alterations per nerve-cell or glia sample and of microelectrophoretic analyses, the base-ratio composition of newly formed or lost RNA (ΔRNA) was computed.

TABLE 6. Microelectrophoretic Analyses of Composition of Glial RNA in Globus Pallidus of 6 Cases of Parkinson's Disease (Purine and Pyrimidine Bases in Molar Proportions in Percentages of Sum). Amount of RNA Increased from 17 (± 1.7 $\mu\mu\text{g}$ /glial sample (Controls) to 34 (± 2.2) $\mu\mu\text{g}$ /glial sample (Parkinson)

	CONTROLS	PARKINSON	Δ RNA FRACTION
Adenine	19.0 \pm 0.78	30.8 \pm 0.70	42.4 \pm 3.19
Guanine	29.1 \pm 0.15	20.3 \pm 0.90	11.5 \pm 2.75
Cytosine	33.7 \pm 0.72	33.2 \pm 1.70	32.8 \pm 3.45
Uracil	18.2 \pm 0.36	15.7 \pm 0.60	13.3 \pm 1.25
$\frac{G + C}{A + U}$	1.69 \pm 0.044	1.15 \pm 0.047	0.79 \pm 0.093
$\frac{A}{U}$	1.05 \pm 0.048	1.96 \pm 0.087	3.18 \pm 0.384
No. analyses:	23	32	
No. cells:	4,600	4,800	

(From Gominato and Hydén, 1963)

TABLE 7. Microelectrophoretic Analyses of Composition of RNA in Nerve Cells in Globus Pallidus of 6 Cases of Parkinson's Disease (Purine and Pyrimidine Bases in Molar Proportions in Percentages of Sum). Amount of RNA Increased from 116 (± 5.3) $\mu\mu\text{g}$ /nerve cell (Controls) to 145 (± 6.3) $\mu\mu\text{g}$ /nerve cell (Parkinson)

	CONTROLS	PARKINSON	Δ RNA FRACTION
Adenine	18.3 \pm 0.42	20.7 \pm 0.65	30.3 \pm 5.0
Guanine	30.5 \pm 0.44	28.8 \pm 0.25	22.2 \pm 3.53
Cytosine	35.3 \pm 0.60	34.4 \pm 0.79	30.8 \pm 5.02
Uracil	15.9 \pm 0.36	16.1 \pm 0.38	16.7 \pm 2.16
$\frac{G + C}{A + U}$	1.92 \pm 0.038	1.72 \pm 0.042	1.13 \pm 0.185
$\frac{A}{U}$	1.15 \pm 0.037	1.29 \pm 0.051	1.82 \pm 0.380
No. analyses:	31	39	
No. cells:	310	300	

(From Gominato and Hydén, 1963)

In a learning situation, the RNA synthesized in neurons and glia involved in the activity leading to the behavioral change was characterized in one case by a DNA-like composition and in another case by asymmetry, high adenine values, and low $\frac{G + C}{A + U}$ values compared to those of ribosomal RNA. To judge by these parameters, the Δ RNA synthesized in cortical and brain-stem neurons and glia in learning is of a chromosomal type. It is to be noted that in learning the trend of the RNA changes is the same in neurons and glia. By contrast, in the cases investigated we found that upon physiological and chemical stimulation the RNA content of the neurons increases and that of the glial RNA decreases. The new RNA formed was characterized by a base-ratio composition typical for ribosomal RNA.

The RNA response of neurons and glia in a learning situation not encountered before is thus quite specific. It seems that the environmental factors instrumental in learning can produce a stimulation of the genome of the glia and the neurons engaged.

In a case of chemical stimulation, the increase in the RNA content of the neuron could be matched by a corresponding decrease in the RNA in the glia immediately surrounding each neuron. The base-ratio composition of the neuronal and glial Δ RNA was identical. This brings up the possibility of a transfer of RNA between glia and neurons. It must be pointed out that only a successfully carried out experiment with labeled RNA may solve this problem definitely.

Finally, a case of biochemical error involving the RNA of the glia (Parkinson's disease) is discussed. The characteristics of the Δ RNA produced in the glia at an early stage of the disease are taken to reflect a release of undesirable genomic activities at a crucial period of the life cycle.

Roche: In the stimulation experiments, the change is not a difference between the control and the experiment?

Hydén: No, it is the composition of the

additional RNA being formed by the cell under the influence of the chemical substance.

To summarize these results, they seem to mean specific biochemical response in neurons and glia at an early stage of learning, and a response that is different from the RNA response to other physiological and chemical stimulations.

In the transfer-of-handedness experiments, the results were rather clear-cut with respect to the composition of the RNA being formed. The high adenine-to-uracil ratio that we found in the balancing experiment when we analyzed the nuclear RNA produced in the vestibular nerve cells cannot be ascribed to a contamination of the RNA being formed by ribosomal RNA. That is impossible. Therefore, in both cortical and brain-stem neurons the RNA analysis suggests that transcription of only one of the two strands of DNA has occurred at specific loci on the establishment of the new behavior. In other words, if an animal is faced with a situation that it has not encountered before and that requires learning, a differential transcription seems to occur at the genetic level in the brain cells engaged, and we are now trying to characterize the RNA synthesized in competition experiments.

Since the tasks we chose were clearly within the capacity of the species, the results point to a selective mechanism that operates in the neurons at the genetic level. The immediate task now is to analyze the end products, the proteins. So let us assume for the sake of discussion that, to speak of a mechanism at the molecular level, proteins in neurons and glia produced by a selective activation of specific gene loci in the learning process facilitate certain neuronal pathways necessary for learning and long-term memory. In other words, a selective mechanism operates.

If this is the basis also for our intellectual process in its highest form—insight learning—then we can of course pose certain direct questions, even if they contain truisms. At what age, for example, should a certain part of the genome be activated in a child by external

stimulation to give the maximal results in abstract thinking? At what age for linguistic training? This would mean that the very same potentialities were present in the brains of our ancestors who fought hard with clubs for their mere existence. They were certainly capable of learning Boolean logic. But to some it would seem pessimistic that, intellectually speaking, we should be fixed in a cast given by the genes; the next question, therefore, is whether there might be an instruction mechanism at the molecular level that would persist only during the life cycle and would consist of remaining conformational changes of proteins following instructional changes of RNA by external factors. This mechanism would exist, of course, in addition to the selective genetically programmed activity. But here, it seems at present, all that can be done is to formulate the question.

Jerne: All cellular biologists have for a long time admired Dr. Hydén's work and his penetrating analysis of the RNA turnover in single neurons of the brain, and I have followed with great interest his beautiful experimental work and his intelligent approach to the fascinating problems of memory and learning.

This morning I was particularly interested in his informal remarks about selection *versus* instruction both in antibody formation and in learning processes by the central nervous system, and also in his demonstration that learning is accompanied by the appearance of a species of RNA in nerve cells that reflects the nucleotide composition of the DNA already present in the genome.

In this connection, I should like to draw attention to a paper by Socrates called "Menon," which was edited by Plato and published in Athens 375 years before Christ. Since Hippocrates was quoted last year, it might be appropriate this year to evoke Socrates in order to confirm again our basis in Greek culture.

The point of view expressed by Socrates in this paper contrasts markedly with the ideas of John Locke, who considered the brain as initially a blank sheet of paper, as in the passage Dr. Magoun quoted. In his paper, Socrates ap-

proaches the question whether learning is possible, particularly whether one can learn the truth. And—rather astonishingly, perhaps—he comes to the conclusion that it is impossible to learn the truth. He says that either the truth is already present in the individual, and in that case it cannot be learned, because one cannot learn what one already knows, or the truth is not already present in the individual, and in that case it cannot be learned, because one could not recognize it if it should arrive. He concludes, therefore, that all learning represents a recollection of elements already present in the individual.

This seems to me quite a remarkable analysis for that stage of Western culture, and I think there is some correspondence between the conclusion Socrates comes to and the finding of Dr. Hydén that the RNA produced during learning reflects the already existing DNA of the genome, which suggests that learning makes use of elements of nucleotide sequences already present in the cell.

Dubos: Professor Hydén, how do you deal with the fact that a living creature that responds constantly to its environment, to the stimuli that impinge upon it, must always be learning? In the sense in which you use the word *learning*, isn't it necessary to assume that what you are doing experimentally is accelerating reactions that are taking place all the time?

To complete my question, would a comparative study of animals undergoing sensory deprivation sharpen the differences you have observed?

Hydén: You have brought up a very important question. Of course, the rate of synthesis in a neuron at the point of contact could influence the whole behavior; but that, I think, would be the rate of synthesis of compounds already present. If there is a new combination of something, that could account for a specificity of a new pathway being opened, so to speak, but the gradation of function—the functioning more or less—could be reflected in the rate of synthesis of a transmitter substance, or of some other unknown proteins, for example.

You asked about deprivation. Fifteen years ago Dr. Brattgard made the following experiments at our laboratory for his thesis: He reared young rabbits completely in the dark, and then he analyzed the ganglion cells of the retina. He used the methods we had at that time, which were not so refined—mostly X-ray spectra photometry at a wave length of about 10 to 12 angstrom, and also some simple RNA analysis. What he found was that, in comparison with those of seeing animals, which had been exposed to stimuli, the cells were about the same size but had a higher water content, a lower protein content, and a very small content of RNA. His conclusion, of course, was that adequate stimulation was necessary for biochemical differentiation of the cells. But this is still with respect to a so-called selective mechanism, Dr. Dubos. The question of the instruction mechanism remains.

Dubos: Would it not be easier to account for the results you have presented by assuming that the selective training, the selective process of learning, consists in preventing the expression of some of the DNA formula so as to bring about selectivity? Under the influence of the ordinary stimuli to which we are subjected, all sorts of things go on and the result is random distribution, whereas with learning there is selective production.

Hydén: Only experimentation could answer such a question. That is a possibility, of course. It would go well with the current lines of certain electroneurophysiologists—that inhibition is the most important functional part in the brain. I should like to be able to present the results of an animal first at the beginning of its life cycle and then later on, to see whether it would respond with the synthesis of more sophisticated molecules—let us say RNA—in the neurons or whether, as you say, the mechanism would be selective in the sense that fewer and fewer parts of the genome would be expressed, but at a higher rate. We have taken up this question; we have experiments going on in which, as Kretsch did some years ago, we put one group of rats in small, dimly lighted cages,

within hearing of the other animals, and a second group in a sort of Luna Park with a lot of smorgasbord that they can help themselves to.

Chagas: Allow me, Dr. Hydén, to add my name to the long list of those who have already congratulated you on your remarkable work.

Last year, I was at a congress on the brain and consciousness, and I was then surprised at the fact that the molecular approach to this problem is still a relative rarity in neurobiology, despite the vivid impression it has generally produced. I myself have a certain doubt about it, concerning the time elements in your theory. Of course, they appear to be quite satisfactory, in principle, for long-term memory; but there are several cases—for example, those that Dr. Jerne has so picturesquely called “Socratic”—in which the time may be too short for the “turnover” or synthetic processes that would have to take place. Experiments in this direction should be of great interest.

Hydén: Do you mean the biosynthesis of RNA and proteins, which is known to take too short a time to account for experimental behavioral knowledge? With short-term memory, it is known that one can interfere with a learning process, but that after a few hours have elapsed it is no longer possible, and also that the hippocampal area is very important in that respect. We have the old results of Lashley, which show that once a new behavior has been established it is soon delocalized. This term *delocalization* is not very well understood, but it becomes clearer if we view it in terms of millions of cells in which a certain change has occurred, and if memory is broadly defined as change by use. I think the time is really sufficient: let us say a couple of minutes for a macromolecular synthesis. Professor Dubos could comment further on that, I am sure.

Dubos: My colleague Dr. G. Edelman told me that at a meeting in Boston last week someone reported (perhaps it was his own work) that at any given time some 150 to 200 different proteins can be recognized, can be clearly differentiated, in the brain. I was wondering whether, if one could determine the change in

distribution of the various proteins with time, one could not obtain thereby some evidence about the rate at which those chemical events you speak of take place during the process of learning.

Hydén: There are some new data I that have not discussed because we are in the midst of analyzing them. Dr. Blake Moore has found protein—perhaps a group of proteins, but it cannot be more than a very few—of an acidic type that he considers to be typical for brain. He has found them in many species and has seen that they cross-react. He has purified them, and I have some. I have also got from Dr. Levine, at Brandeis University, antibodies he has produced against what we might call the Moore protein, which is very acidic and moves very fast in an electrophoresis, like that of the albumins.

What I have done to begin with is to see whether it is produced by the neurons or by the glia. I can't answer this question, but I can say that I have been able to localize it in neurons. I am using the microcapillary technique with acrylamide gels for electrophoresis—using that as an immune chemical means both with and without antibodies, to see which band is present and which was removed. It certainly is produced in the neurons. But that would mean a rather limited group of proteins—not 200, if it is now true that that is specific for the proteins. Dr. Moore states that the concentration of it in the brain is ten thousand times greater than in the liver and other organs.

Chagas: I was so impressed by the technique described that I may have failed to grasp its full significance. My question now is whether the difference of values found for different isolated neurons is not a result of experimental error. Also to be considered, of course, is

whether the composition of the neurons taken from the same area is more or less constant.

Roche: I gather that analyses of RNA, composition, and so on in glia and neurons parallel each other—that during the learning process the changes in glia are the same as in neurons. Was this expected, and does it lead to any comment as to their relative or respective function in the learning process?

Hydén: To answer Dr. Chagas first, the coefficient of variation in the values is around 5 per cent, about the same as the experimental error. With precisely his question in mind, we have performed a closer statistical study on one part of the nervous system, the inner ear and the bipolar ganglion cells there, and we found that around 12 per cent constituted the intra-group variation. The experimental error could be kept at 5 to 7 per cent.

Now for Dr. Roche's question about the parallel reaction of neurons and glia. That was not expected in the learning process because of our previous experimental background. When we performed physiological stimulation of the vestibular area, and again in stimulation with chemical compounds, we found inverse changes: when protein synthesis or enzyme activities went up in the neurons, they decreased in the glia. So that was what we expected. But in these learning experiments we have found the results in neurons and in glia to be the same.

Moderator: Let us move now from the neural units and their component chemistry to exploring the aggregate neural systems making up the brain and, in particular, to considering "Current Concepts in the Neurophysiology of Learning." It is a great pleasure, personal as well as formal, for me to ask Dr. Hernández Peón of the Institute of Brain Research, Mexico City, to make his presentation.

CURRENT CONCEPTS IN THE NEUROPHYSIOLOGY OF LEARNING

Raúl Hernández Peón

The intriguing nature and potentialities of learning have always aroused the interest of philosophers and scientists. This brief review of the main current neurophysiological findings and concepts of learning is intended to convey basic information to unspecialized scientists, and therefore necessarily involves many omissions. Along with a synthetic description of the neural correlates of learning, some personal hypotheses will be advanced that may foster research in this field.

Learning is one of the most pervasive and fundamental biological processes observed throughout the animal scale. Although it is commonly accepted that learning implies the acquisition of information that tends to modify innate or already acquired performances of the organism, the great number of definitions proposed for this term reveals the difficulty in assessing the essential nature of the underlying mechanisms. The enduring changes produced by learning are usually associated with adaptive behavior. But in some instances it may contribute to maladjustments of the individual.

Because of the ubiquity of learning in organisms of every grade of evolution, the conclusion seems warranted that it derives from a fundamental property of living matter and therefore does not necessarily require special complex neuronal circuits. To designate the property concerned with enduring neural changes we have adopted the term *plasticity*, proposed by Konorsky (1948), thus establishing a distinction between it and another fundamental property of living cells, *excitability*, which is related to very transient and reversible changes produced by the stimulus. Granting that through specialization of function both plasticity and excitability developed more in certain elements of multicellular organisms, there is no doubt that the nervous system is endowed with both properties. In animals with

nervous systems in which "all or none" signals are transmitted, plasticity permits the storage of information delivered by those signals, whereas excitability is concerned with their generation and transmission. Furthermore, it seems obvious that, through the evolution of the nervous system, some neurons developed longer and more excitable axons for transmission than other short-axon non-propagating elements. From the observation that the former type of neurons do not present enduring plastic changes upon stimulation, whereas the latter are essential for those changes, the hypothesis of an evolutionary differentiation of excitable and plastic neurons within the central nervous system may be safely conjectured.

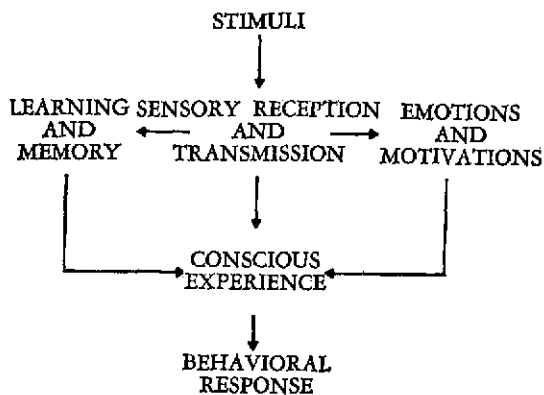
Since nothing is known about the ultimate nature of plasticity, our knowledge about the neural plastic change associated with learning derives mainly from the indirect changes of excitability currently assessed by electrophysiological techniques. For discussion of the main neurophysiological correlates of learning it is necessary to establish a general classification of the fundamental types observed from Protozoa to man. First of all, learning may be divided into negative and positive. Negative learning leads to decrement or disappearance of a response previously evoked by a given stimulus; positive learning involves the acquisition of a response to a stimulus that did not elicit it before. The elimination of irrelevant responses during negative learning is not a passive phenomenon but depends on central processes that actually prevent them from appearing as they otherwise would. This active restraining process has been termed *plastic inhibition* (Hernández Peón, 1960) in order to distinguish it from Sherringtonian transient inhibition. On the other hand, the acquisition or enhancement of responses during positive learning requires the establishment or facilitation of neural connec-

tions by a process designated *plastic association* in this modern terminology (Hernández Peón, 1957). Plastic inhibition is probably the primary and most important process in learning; without it animal behavior would be disorganized and adaptation of the organism to the external environment would be impossible. Plastic inhibition is so important for normal functioning of the central nervous system that it may be no exaggeration to say that while plastic inhibition may develop in the absence of plastic association, the latter is always accompanied by the former.

According to their complexity, the following types of learning may be considered: (a) habituation; (b) classical conditioning; (c) instrumental conditioning, or trial-and-success learning; and (d) latent learning. To these, a separate variety of learning produced in newborn animals or certain species by a single exposure to a stimulus and termed *imprinting* may be added. A number of neurophysiological studies carried out during the past decade have contributed to an initial understanding of the functional role of various brain regions in certain types of learning and other related processes taking place before, after, and simultaneously in the central nervous system. The main functional operations that take place between the stimulus and the behavioral response are summarized in Figure 1. All types of stimuli initiate a series of events starting from sensory reception at the receptor level and followed by sensory transmission along all the levels of the central nervous system, both at specific and at non-specific or polysensory pathways. Afferent impulses are thus conducted to neural systems involved in emotions, motivation, learning, and memory. In turn, the impulses coming from those neural circuits are conveyed to a highly specialized neural system concerned with sensory integration and conscious experience. Finally, after the activation of decision-making mechanisms, the adaptive behavioral responses occur.

Habituation. Habituation, the simplest type of learning (Thorpe, 1950), consists in an enduring, progressively oscillating decrement of

Figure 1. DIAGRAMATIC REPRESENTATION OF MAIN NEURAL PROCESSES INVOLVED IN MOST BEHAVIORAL RESPONSES



responses produced by monotonous repetition of a stimulus that loses significance for the organism. This pervasive phenomenon is observed not only in effector responses but also in sensory experiences, as everybody can confirm in everyday life. A logical question to ask is, What changes occur in the central nervous system during habituation that may account for all its manifestations? Recordings of the electrical activity of the neuroaxis in unrestrained animals with electrodes permanently implanted have disclosed neural correlates of habituation both at the specific and at polysensory systems in the brain and spinal cord. The terms *afferent neuronal habituation* and *neuropil habituation*, respectively, have been proposed for designating each process (Hernández Peón, 1960).

Neuropil habituation is accompanied by decreased excitability of the neural pathways where impulses of various sense modalities converge. This has been shown by recording the background or ongoing activity of the brain and the activity evoked by brief sensory or electrical stimuli. Indeed, by monotonous repetition of a stimulus, the originally diffuse evoked potentials diminish in amplitude and tend to remain restricted to the specific afferent pathways. But if the intermittent rhythmic stimulation is prolonged enough, blocking of sensory transmission can be observed within the specific afferent pathway itself, as will later be discussed. Per-

haps the most basic manifestation of neuropil habituation is that concerned with the arousal reaction. In this regard, it is interesting to point out that not only does monotonous repetition of a stimulation that at first elicits a prolonged EEG desynchronization tend to produce progressively shorter arousal reactions until its disappearance, but subsequent presentations of the same stimulus elicit the EEG synchronization characteristic of the initial state of sleep. A clear cause-effect relationship between habituating stimuli and EEG signs of sleep was obtained from experiments in which flashes of light were monotonously repeated and the electrical activity from the visual cortex was recorded. After a number of stimuli, each photic-evoked potential was followed by a spindle burst. Furthermore, when the flashes were suddenly stopped, the spindle bursts nevertheless appeared at the same interstimulatory intervals during a brief post-stimulatory period (Hernández Peón, 1960). This experiment additionally indicated that the nervous system is intrinsically capable of reproducing the temporal sequence of events produced by a given stimulus, a power that has usually been designated "conditioning to time."

The manifestations of habituation occur not only at polysensory pathways but also at all the levels of the specific afferent pathways. This phenomenon, called *afferent neuronal habituation* (Hernández Peón *et al.*, 1957; Hernández Peón, 1960), is first seen at the cortex; later it extends down to the first sensory synapse and to pre-receptor mechanisms that are known to reduce the intensity of sensory stimuli before impinging upon sensory receptors. Habituation at the lowest sensory synapse was first demonstrated by Hernández Peón and Scherrer (1955). They found that auditory potentials recorded from the cochlear nucleus and evoked by pips decreased in amplitude following a waxing and waning course after monotonous repetition of the acoustic stimuli. This result was immediately confirmed by Galambos *et al.* (1956) and more recently by Velluti *et al.* (1964), Webster *et al.* (1965), and Buño *et al.* (in press).

Similar habitatory changes have also been observed in the visual (Hernández Peón, 1955; Hernández Peón *et al.*, 1958), tactile (Hernández Peón and Brust Carmona, 1961; Hernández Peón *et al.*, 1962), and olfactory pathways (Hernández Peón, 1960, 1961). The demonstration that this decrement was not the result of fatigue but was a specific type of learning related to the particular testing stimulus was provided by several experimental procedures provoking dishabituation. Indeed, recovery of the evoked potentials was produced by sudden presentation of a novel alerting stimulus (Hernández Peón, 1955), by barbiturate anesthesia (Hernández Peón *et al.* 1957), by extensive lesions in the midbrain tegmentum, or by Pavlovian conditioning. The later results represent experimental evidence for the contention that the control of sensory impulses by efferent mechanisms operates according to the significance of the stimulus. Indeed, once acoustic habituation had been established in a cat, if the pip to which it had become habituated was associated with a nociceptive electric shock applied to one limb, the auditory-evoked potentials were remarkably enhanced after a number of associations (Hernández Peón, 1955; Hernández Peón *et al.*, 1967; Galambos *et al.*, 1956).

By the same token, sensory rhythmic discharges induced in the olfactory bulb by puffs of fish odor diminished in a waxing and waning course after the stimulus was monotonously repeated. If the cat was allowed to eat the fish, however, the next stimulus thereafter elicited an olfactory response; this disappeared again when the odor was not reinforced by the presentation of food (Hernández Peón *et al.*, 1957; Hernández Peón, 1960).

The question arises whether the plastic changes produced by habituation can occur in the lowest level of the central nervous system separated from higher structures, since it has been usually assumed that plasticity is an exclusive privilege of the cerebral cortex. In order to answer this question, potentials evoked by tactile stimuli applied to the skin were recorded from the spinal cord in decerebrated cats. These

potentials were found to diminish in amplitude in an oscillating manner after regular repetition of the stimuli (Hernández Peón and Brust Carmona, 1961). At this time, a high spinal transection that separated the spinal cord from the rest of the brain resulted in an enhancement of the potentials, which showed that descending inhibitory influences of brain-stem origin play a role in this phenomenon. However, when the tactile stimulus was repeated again, the potentials diminished. It may therefore be concluded that habituation and its associated plastic changes can take place in the isolated spinal cord. Habituation of sensory responses has also been observed in humans by recording from the scalp, with averaging techniques, potentials evoked by auditory (Bogacz *et al.*, 1961), visual (Bogacz *et al.*, 1961; García Ausst, 1963), or tactile stimuli (Hernández Peón, 1964a).

On the basis of the available evidence, the following neurophysiological mechanisms may be proposed to account for the various manifestations of habituation.

1. Sensory or non-sensory activation of neurons within the diffuse polysensory pathways extending throughout all the levels of the central nervous system tend to produce recurrent inhibition of the same neurons, possibly by short collateral circuits involving inhibitory interneurons.

2. Rhythmic sensory stimulation elicits a progressive recruitment of hypnogenic neurons along a recently disclosed "Sleep System," which in turn inhibits the arousing neurons of the "Vigilance System."

3. Prolonged repetition of non-significant stimuli activates inhibitory mechanisms at the brain stem that partially block the entrance of afferent signals to the central nervous system ("sensory filtering") and their transmission to higher levels. Independently, centrifugal mechanisms acting upon peripheral pre-receptor effectors reduce the intensity of sensory stimuli.

Classical conditioning. The work of the Russian school created by Pavlov has established that by adequate timed pairing of an indifferent

stimulus with one that elicits various somatic or autonomic responses (unconditional stimulus, US), the former (conditional stimulus, CS) acquires the capacity to elicit similar responses (conditioned responses, CR). Pavlovian conditioning may be said to represent the simplest type of positive learning. Positive learning requires plastic association of neural activities induced by the unconditional and the conditional stimuli. When the effects of this procedure are studied, it becomes evident that the earliest conditioned responses are elicited by the environmental stimuli associated with the US. It is only after most of the conditioned responses to the environment are extinguished that the animal learns to respond selectively to the experimental CS. Obviously, two different processes are involved in this sequence of events, which leads to the following basic questions: (a) What is the locus of the plastic association responsible for the acquisition of conditioned responses? (b) What are the neural events that underlie the selection of a given conditioned response and the extinction of irrelevant response? Since Pavlov, it has been assumed that the cerebral cortex is the site of the plastic association (which he called temporary connections). But it has been demonstrated, contrary to the classical Pavlovian assumption, that ablation of the "cortical analyzers" and even total ablation of the neocortex does not prevent conditioning. On the other hand, small subcortical lesions at the midbrain level seriously interfere with the earliest plastic associative changes of conditioning (Hernández Peón *et al.*, 1958). In another experimental study designed to test the functional participation of cortical and subcortical structures in the earliest manifestations of positive learning, two types of conditioned responses were established in each animal; an alimentary reflex (salivation) to the visual presentation of food, and a flexor reflex produced by an electric shock associated with a buzzer. After a lesion was made in the midbrain tegmentum without interfering with consciousness, both the alimentary and the flexor conditioned responses disappeared. The condi-

tioned responses persisted, however, after ablation of the neocortical mantle (Hernández Peón and Brust Carmona, 1961). It is evident that the brain stem plays a more important role than the cortex during the earliest phase of conditioning. These observations, emphasizing the importance—which has been neglected—of subcortical structures in conditioning and learning, have been supported by data derived from modern electrophysiological techniques. Indeed, electrical recordings from the brains of experimental animals during classical conditioning (Galeano, 1963) have revealed the following changes:

1. A generalized neocortical EEG desynchronization appears prior to the behavioral conditioned response.

2. During this early phase the potentials evoked by the CS appear widespread throughout the polysensory system and can be recorded all over the cortex and from numerous subcortical structures (Marsh *et al.*, 1961). However, the earliest increase of excitability has been detected at the mesencephalic reticular formation both by the appearance of conditioned specific frequency responses (John and Killam, 1959, 1960) and by a significant reduction in the recovery cycle of reticular evoked potentials (Buser *et al.*, 1958).

3. A rhythmic theta rhythm of 4.6 c.p.s. appears in the hippocampus and entorhinal cortex simultaneously with the orienting reaction.

4. The initially generalized EEG neocortical desynchronization and the enhanced potentials evoked by the CS become localized to the cortical area, corresponding to the specific afferent pathway activated by the US. Microelectrode recordings performed during conditioning have confirmed and extended the studies of macro-potentials. In fact, polyvalent units in the reticular formation were most readily affected by conditioning (Yoshii and Ogura, 1960), and at the stage of localized desynchronization the CS affected only the corresponding cortical neurons and some thalamic neurons that had been unresponsive prior to conditioning.

5. The hippocampal response disappears in later stages of conditioning.

The neural facilitation produced by conditioning can be detected at a level as far down as the retina, as shown by Palestini *et al.* (1959). Evoked potentials produced by a series of four flashes of light were recorded from the optic tract. The potentials produced by the third and fourth flashes were smaller than those produced by the first two flashes. After the flashes of light were associated with an electric shock applied to one limb of the animal, the potentials produced by the third and fourth flashes were enhanced. As has been observed at the cortical level, the electrical manifestations of conditioning at the first sensory synapse could be extinguished and disinhibited. When only the flashes of light were applied, not reinforced by the electric shocks, the photic potentials decreased. They recovered when the electric shock was again applied. Therefore, the sensory manifestations of conditioning follow the same principles as the effector conditioned responses studied by the Russian school.

All these observations provide an experimental basis for the following interpretations:

1. The polysensory system, not the specific afferent systems or Pavlovian analyzers, play a fundamental role in plastic association during conditioning.

2. The earliest plastic associative changes occur at the brain-stem reticular formation. This should not be surprising in view of the essential participation of the rostral brain stem in arousal and alertness, as demonstrated by Magoun and his associates (Magoun, 1963).

3. While the cerebral cortex is not necessary for plastic association during the earliest phase of conditioning, the integrity of the mesencephalic reticular formation is essential at this time.

4. Polyvalent reticular units responding to several modalities seem to be particularly important in forming the initial connections.

5. The earlier dominance of the mesencephalic reticular formation is later shifted to the

thalamic levels, which allows more selective cortical effects.

6. At this stage, the hippocampal system becomes activated and possibly influences the reticular formation by inhibitory interactions. As will be discussed below, it is not far-fetched to assume that the hippocampal formation plays an important role in the integration of present and recently past experiences.

7. The plastic facilitatory changes produced by conditioning can be detected at all levels of the central nervous system, including the first sensory synapse.

An intrinsic plasticity of the cerebral cortex has been demonstrated by studies with direct current polarization. Conditioning to a tone has been shown to occur when anodal polarization is applied to the motor cortex (Rusinov, 1953), and interference in performance of a motor CR to a flicker has been observed during and after negative polarization at the visual cortex (Morrell and Naitoh, 1962). Furthermore, a chronically isolated cortical slab displaced specific rhythms of a stimulus applied before tetanization when a stimulus of another frequency was presented, as though the cortex had retained a "trace" of the previous stimulation (Chow and Dawson, 1964). By the same token, there are studies indicating plastic facilitation in the isolated spinal cord.

It may be concluded that plastic association can take place at all levels of the central nervous system from the spinal cord up to the cortex.

Internal inhibition. When the CS is repeated without reinforcement, the CR is extinguished. Electrophysiological recordings have shown that the EEG and the conditioned evoked potentials present similar changes during extinction and habituation. During extinction, differentiation, delayed inhibition, and supramaximal inhibition, the negative conditional stimulus acquires cortical synchronizing properties. This may be the result of different degrees of activation of central hypnogenic mechanisms. By the use of localized chemical stimulation of the central nervous system, it has recently been found that

acetylcholine elicits all the electrophysiological and behavioral manifestations of sleep from a very well circumscribed anatomical pathway termed Sleep System (Hernández Peón *et al.*, 1962, 1963; Hernández Peón, 1964a, 1965b). This pathway is composed of two segments: an ascending limb originating at the spinal cord and passing through the medulla oblongata and pons in order to act upon the midbrain Vigilance System; and a descending component arising from certain cortical areas, such as the anterior cingulate gyrus, the orbital surface of the frontal lobe, and the pyriform cortex of the temporal lobe. All these corticofugal fibers join a limbic-midbrain circuit in the preoptic region formed by the medial forebrain bundle, the ventromedial part of the midbrain, the interpeduncular nucleus, and Bechterew's and Guden's nuclei. This descending pathway appears to extend down to the region of nucleus reticularis giganteo-cellularis in the rostral medullary tegmentum (Hernández Peón, 1965c).

Just as changes in the electrical activity of the brain are detected before the behavioral conditioned response appears, during extinction those changes persist beyond the disappearance of the behavioral response.

External inhibition. The blocking of a conditioned response produced by an alerting novel stimulus is accompanied by EEG desynchronization and reduction of the evoked potentials related to the CS both in polysensory structures and in the corresponding specific afferent pathway as far down as the first sensory synapse. Therefore, external inhibition may be identified with distraction from the CS and all its associated neurophysiological mechanisms.

Instrumental conditioning. This term is used to designate a training procedure by which the animal learns to perform an arbitrarily selected behavioral response normally present in its repertoire, which is followed by a reinforcing or rewarding situation—either the satisfaction of needs for food or water or the termination or prevention of a noxious stimulus. In this type of learning, performance of the conditioned somatic response alters the external environment

and is "instrumental" in achieving the organism's motivational goal. So far, no visceral responses have been conditioned by this procedure. If somatic instrumentally conditioned responses are dependent on the central mechanisms involved in voluntary behavior, as is usually assumed, it is doubtful whether autonomic responses might be instrumentally conditioned.

During the early phase of experimental instrumental conditioning the animal performs a series of unsuccessful trials until the correct performance is fully apprehended. That is why this type of learning has also been termed *trial and error*. However, the term *trial and success* is more correct, because the animal learns by success and not by error.

Many tasks of different complexities have been devised by experimental psychologists using the fundamental principle of instrumental conditioning, and the effects of localized cortical ablations on acquisition, retention, and performance have been studied. More recently, it has been found that subcortical lesions in several limbic regions, such as the hippocampus, the amygdaloid complex, and the septum, interfere with some aspects of the learning processes. The results can hardly be interpreted unequivocally because of the multiple factors involved.

Electrophysiological studies of instrumental conditioning made in recent years have demonstrated significant changes in widespread structures of the polysensory system during this type of learning. For instance, with the initiation of avoidance conditioning to flickering light, a marked increase in frequency-specific activity occurs in visual and auditory cortex, reticular formation, superior colliculus, and lateral geniculate but not in amygdala, hippocampus, and n. ventralis anterior of the thalamus (John and Killam, 1959, 1960). Early in conditioning the hippocampus begins to respond, and later the specific frequency responses appear in n. ventralis anterior. It is therefore evident that a particular sequence of events occurs in different neural structures during the temporal development of learning. It is interesting to note that

in differential approach-avoidance conditioning the frequency of the electrical responses in the specific and polysensory systems corresponds to that of the CS when the behavioral response is correct, whereas during incorrect performances the frequency of the electrical responses in the polysensory structures corresponds to that of the CS for which the behavioral response would have been correct (John, 1963). Other experiments support the view that changes of macro-potentials like those mentioned above are related to the processing of signal-derived information by these structures. The introduction of average response computation and signal analysis methods has recently permitted the study of waveshape detail during instrumental conditioning (John *et al.*, 1963; John, 1964). In brief, it has been found that as informational significance is attached to conditional stimuli, the corresponding evoked potentials in widespread regions of the brain become highly similar in waveshape. These data support the view that learning involves the formation of anatomically extensive functional circuits in which several levels of the brain are temporally coordinated in a highly specific fashion.

Attentional and motivational factors certainly play an important role in facilitating plastic associations in instrumental learning. Reserving "attention" for a later discussion, it can be stated that motivation is essential for the acquisition of instrumental conditioned behavior but is unnecessary for establishing classical conditioned responses. This has been shown in conditioning produced by using direct electrical stimulation of the cerebral cortex as CS and US (Doty and Giurgea, 1961). However, motivation tends to facilitate the simplest plastic association of conditioning by lowering the threshold of the sufficient CS (Miller, 1961).

One of the main contributions to psychophysiology during the last few years was made by Olds (1962), who showed that when an electrode is implanted in certain parts of the brain and is connected to a stimulator that can be activated by the animal, the animal tends to stimulate his own brain. But when the

electrode is placed in some other regions of the brain and the animal presses the lever once, he avoids it from then on. These findings led to the conclusion that there is a positive reinforcing system, localized in the limbic system, and a negative reinforcing system that corresponds to midline structures in the diencephalon and midbrain. If we follow all the anatomical pathways involved in reward and punishment, we find that they correspond to two neural systems described many years ago by Le Gros Clark (1938), known as the medial forebrain bundle system and the periventricular system. The former is related to reward or positive reinforcement, and is laterally located in the forebrain and hypothalamus; the latter is related to punishment or negative reinforcement, and is medially located in the mesodiencephalon. When a stimulus activates a sensory-motor pathway in order to produce a given response, and the response is followed by a reward, the positive reinforcing system is activated, which in turn facilitates the sensory-motor structures involved in that response. If, on the contrary, the response is not followed by a reward, or is followed by punishment, the negative system is activated, which in turn inhibits the sensory-motor structures involved in the production of a future response to the same stimulus (Stein, 1964).

Latent learning. This term has been used to denote learning without patent reward. Actually, the information derived from latent learning is embraced by the common term *memory*. The neurophysiological problem of memory and its associated consolidation process cannot be divorced from the antecedent carrying information process. A fundamental factor for the establishment of learning is the reception of sensory information produced by environmental stimuli, and this process is strictly related to attention. In this regard, there is no doubt that better-attended-to stimuli leave more stable and accessible memory tracings than those outside the span of attention. It is well known that the span of attention is limited and that therefore we can only attend to or perceive a small

number of sensory stimuli at any given moment. Only the stimuli within the focus of attention are clearly and distinctly perceived by the subject, whereas those on the fringe of attention are less clearly perceived (Hernández Peón, 1964a). Furthermore, there are some stimuli outside the fringe of attention that are not consciously perceived but seem nevertheless to leave memory tracings in the brain.

It has been shown in recent years that selection in attention is strictly related to neural processes that filter the entrance of sensory signals to the central nervous system and regulate their succeeding transmission (Hernández Peón, 1961, 1964a, 1965d). Sensory filtering has been demonstrated in the cat at the cochlear nucleus, at the retina, at the olfactory bulb, at the spinal trigeminal sensory nucleus, and at the spinal cord. Sensory regulation has also been observed at subcortical levels of the central nervous system in humans. During recordings made in patients with electrodes implanted in the optic radiations, Hernández Peón and Donoso (1957, 1959) found that the amplitude of photic evoked potentials decreased significantly when the subject was engaged in a mental task such as solving an arithmetic problem. After he had reached the solution the potentials recovered. Simultaneously and independently, Jouvet (1957) confirmed and extended these observations, showing that the photic evoked potentials were enhanced when the subject was asked to count the flashes.

Recent studies in humans in whom averaged evoked potentials recorded from the scalp were correlated with task performances have shown a strict parallelism between the size of the potentials and the performance efficiency. The most significant changes occur in the late components of the evoked potentials corresponding to activation of the polysensory system (Haider *et al.*, 1955). Preliminary studies in mentally retarded subjects have shown an inadequate control of sensory transmission during attention (Hernández Peón, 1964a, b). The attentional changes of tactile cortical evoked potentials were found to lag by approximately forty

seconds, in contrast to the immediate changes observed in normal individuals during comparable situations. These results constitute the first objective evidence that the mechanisms of mentally retarded subjects for controlling the afferent inflow to their brains, and for receiving adequate information on their environment, are impaired.

The question arises whether the controlling mechanisms of attention can be enhanced. In experiments with chemical stimulation of the brain, Hernández Peón *et al.* (1962, 1963) found that after a few minute crystals of carbamylcholine were placed in the septal region of cats, a state that we designated *magnetic attention* ensued. Under these conditions, the cat attentively followed for many seconds any indifferent object, such as a pencil, moving within his visual field. Now, cats are similar in their attention mechanisms to mentally retarded subjects—usually they cannot focus their attention on a given item for many seconds. Therefore, even in animals with a poorly developed cortex the mechanisms of attention intrinsic in their brains can be enhanced. This finding may have some relevance to the problem of mental retardation associated with an impairment of the corticoreticular mechanisms that control attention and therefore an adequate input to the brain.

Besides the information consciously perceived and stored in the brain, there are indications that a great amount of information of which the individual is not aware also leaves memory tracings. In recent years it has been experimentally demonstrated that conditioning can be produced with subliminal stimuli that are not perceived by the subject; nevertheless, they leave memory tracings that can be detected through the conditioned alpha rhythm (Barrat and Herd, 1964). On the other hand, it has been shown that tachistoscopically presented images that cannot be recognized by the subject leave memory tracings later retrievable during dreaming or hypnosis but not during ordinary wakefulness (Shevrin and Luborsky, 1958; Shevrin and Stross, 1962).

Therefore, it may be stated that the brain stores at least two types of information: (a) that arising from sensory receptors that comes to the neocortical analyzers and amplifier mechanisms for later transmittal to the neural system involved in "conscious integration" (Fessard, 1954), which corresponds to conscious sensory perception; and (b) information arising from sensory receptors that arrives at the Memory Systems without passing through the Conscious Experience System. It is likely that a great many inhibitory influences seemingly originating from the Vigilance System in the brain stem restrain the activity of many neural circuits, including both the Recent and Remote Memory Systems and the Emotional and Motivational Systems (Hernández Peón, *in press*). According to this view, waking inhibition is released during dreaming when the Sleep System becomes active and the Vigilance System is maximally inhibited. Whereas the activity of the plastic neurons with memory tracings would underlie the manifest content of dreams, the released activity of the more inhibited Motivational Systems would underlie the latent content of dreams (Freud, 1958). Either the metabolic activity or the synaptic transmitting properties of the inhibitory neurons appear to be depressed by certain drugs, like the hallucinogenic ones. In unpublished experiments, I have confirmed that the Mexican hallucinogenic mushroom *Psilocybus mexicanus* released memory tracings that are strictly related to the person's past experiences in a temporal sequence opposite to that of acquisition.

In brief, from the practical point of view, facilitation of learning requires that four aspects be taken into consideration: (a) the changes occurring at the molecular level during plastic associations; (b) the inhibitory tonic or plastic influences that can be released by certain pharmacological agents; (c) the neural mechanisms of attention; (d) the neural mechanisms of motivation.

If the inhibitory hypothesis of memory is correct, it may open an avenue of research for the scientific study and application of drugs

capable of enhancing memory and mnemonic associations. On the other hand, a better understanding of the neurophysiological mechanisms of attention may find a practical application for increasing the brain capacity to receive selective information. Investigation along these lines might, it is hoped, prove fruitful in the scale of mental activity from mental retardation to creative thinking.

Thompson: Have you any evidence of long-term habituation effects or fatigue effects? That is, have you found a sequence of habituation and dishabituation that over a long series of such trials can be picked up in diminished responsiveness at the electrophysiological level?

Hernández Peón: In all our experiments, we have dealt mainly with habituation in the earlier phases, because the largest changes are produced between the first stimulus to the animal and the following ones. There is a faster rate of habituation in the earlier phase, and then the rate decreases. In a paper in *Science* a few weeks ago, it was shown by an Australian neurophysiologist that the rate of decrement of the habituated responses in the cochlear nucleus is a function of the number of stimuli. This rate of decrement was found to be independent of the temporal pattern of stimulation.

Hydén: I should like to point out a cor-

relation between biochemical data and your data on the reticular formation during sleep. (It very seldom happens that one can point to a correlation.) We found some time ago that in the caudal part of the reticular formation, during natural physiological sleep, the rate of succinoxidase activity was high in the neurons and in the cells, but in the glia, immediately outside, it was low. During wakefulness, when we were certain electrically that the animals were awake, the effect was the opposite—high in the glia and low in the neurons. Perhaps the explanation could be that if there is a damping effect from that, these neurons would be active. But leaving that aside, when we tested barbiturate sleep, we found, as you did, a depression of the respiratory enzyme activities all over this area.

Moderator: These first two papers were designed to present a background for the rest of the program, which is directed toward modifications of psychobiological development by nutritional, psychosocial, and cultural factors. We want to move next to the discussion of nutritional deprivation, and invite initially the presentation of studies in animals. May I ask Dr. Widdowson of Cambridge University to make her presentation.

NUTRITIONAL DEPRIVATION IN PSYCHOBIOLOGICAL DEVELOPMENT: STUDIES IN ANIMALS

E. M. Widdowson

We all know that nutritional deprivation hinders growth of the body, but we know less about its effect on the growth and development of the brain, so I have set myself four questions to answer. First, what evidence have we from studies on animals that nutritional deprivation early in life prevents the normal growth in size of the brain? Second, how far

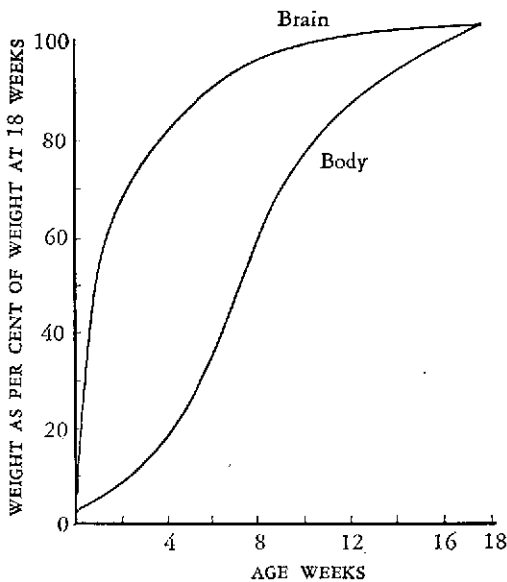
does nutritional deprivation hinder the structural development of the brain? Third, how far can these deviations from normal, if they exist, be put right by rehabilitation on a plentiful supply of a good diet? Fourth, what do we know from animal experiments about the effect of nutritional deprivation on the temporary or permanent function of the brain?

We have made most of our studies on rats and pigs, and I shall use these two species to illustrate my points.

Effect of nutritional deprivation on the growth of the brain

Figure 1 shows the normal growth of the rat's brain compared with the growth of the body. In order to compare the values directly, both brain and body weights have been expressed as a percentage of the value at eighteen weeks

Figure 1. WEIGHT OF BRAIN AND BODY OF RAT AS PER CENT OF VALUE AT 18 WEEKS



weeks. The brain grows extremely rapidly during the first two weeks after birth, and by the end of this time it has reached 66 per cent of its mature size. The body, by this time, is only 8 per cent of its mature weight. The growth of the brain then slows down, and it remains slow all through the time when the body is growing most rapidly—between six and ten weeks, which corresponds to the puberty spurt in man. The importance of showing these curves is that they help to make the next point clear: that the extent to which the size of the

brain is affected by nutritional deprivation depends upon the age when the nutritional deprivation begins. If rats are undernourished from birth by suckling a large number of young, fifteen to twenty, on one mother, the undernutrition coincides with the time when the brain is growing very rapidly in relation to the body as a whole. Undernutrition at this age hinders the growth of the body much more than that of the brain—in fact, it may not hinder the growth of the brain at all—and the brain comes to form an abnormally large percentage of the body weight (Widdowson and McCance, 1960). This is true for the undernourished animal in comparison not only with a well-nourished one of the same age but much heavier, but also with a well-nourished animal of the same weight but much younger (Table 1). If undernutrition begins at three weeks of age, when the growth of the brain has already slowed down and that of the body is accelerating, the growth of the body is still hindered more than that of the brain, but the difference is quantitatively less. Table 2 shows that under our conditions of moderately severe undernutrition for eight weeks the brain of the undernourished animals aged eleven weeks and weighing only 60 grams formed the same percentage of the body weight as those of normal 60-gram animals four to five weeks old (Dobbing and Widdowson, 1965).

We have undernourished pigs severely from early in suckling, so that by the end of a year they weighed only 5 to 6 kg as compared with 160 to 180 kg for a well-nourished litter mate—in other words, they were only about 3 per cent of their expected weight (McCance, 1960). These undernourished animals, of course, have smaller brains than the well-nourished animals one year old, but their brains are very large both for their age and for their size (Table 3). In this respect, therefore, they behave like the rats undernourished from birth. These pigs are far more severely undernourished, in a way, than any of the rats I have described, and they show all sorts of interesting things—large skeletons and very large testicles

TABLE 1. Rats: Effect on Body Weight and Brain Weight of Undernutrition from Birth

	AGE (days)	BODY WEIGHT (grams)	BRAIN WEIGHT (grams)	BRAIN WEIGHT IN RELATION TO BODY WEIGHT (per cent)
<i>Same weight</i>				
Undernourished	10	10	1.0	10
Well-nourished	4	10	0.5	5
<i>Same age</i>				
Undernourished	10	10	1.0	10
Well-nourished	10	25	1.0	4

TABLE 2. Rats: Effect on Body Weight and Brain Weight of Undernutrition from Weaning at 3 Weeks to 11 Weeks of Age

	AGE (weeks)	BODY WEIGHT (grams)	BRAIN WEIGHT (grams)	BRAIN WEIGHT IN RELATION TO BODY WEIGHT (per cent)
<i>Same weight</i>				
Undernourished	11	60	1.45	2.4
Well-nourished	4½	60	1.45	2.4
<i>Same age</i>				
Undernourished	11	60	1.45	2.4
Well-nourished	11	220	1.70	0.8

for the size of the body (Dickerson, Gresham, and McCance, 1964), but muscles that contain as much extracellular water and as little nitrogen per 100 grams as the muscles of a fetal pig (Widdowson, Dickerson, and McCance, 1960). But that is by the way. To recapitulate about the weight of the brain, undernutrition

of any growing animal produces a small brain, but one that forms an abnormally large percentage of the weight of the body for the age. If the undernutrition is imposed early enough in life, when the brain is growing very rapidly relative to the body as a whole, the effect is aggravated and the brain becomes so large a

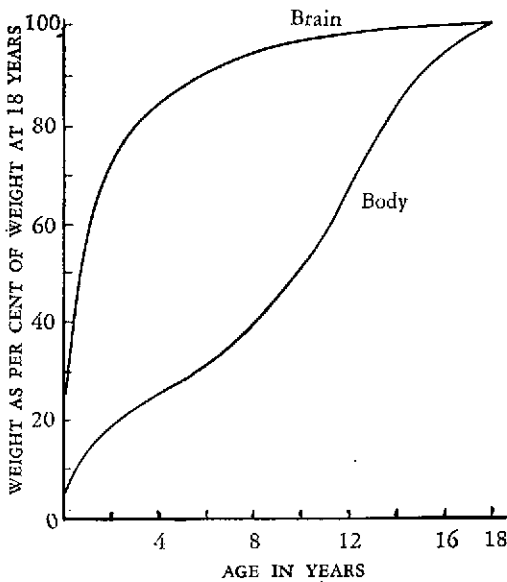
TABLE 3. Pigs: Effect on Body Weight and Brain Weight of Severe Undernutrition from 2 Weeks to 1 Year

	AGE	BODY WEIGHT (kilograms)	BRAIN WEIGHT (grams)	BRAIN WEIGHT IN RELATION TO BODY WEIGHT (per cent)
<i>Same weight</i>				
Undernourished	1 year	5.4	75	1.4
Well-nourished	4 weeks	5.8	47	0.8
<i>Same age</i>				
Undernourished	1 year	5.4	75	1.4
Well-nourished	1 year	156.0	111	0.07

percentage of the body weight that it even exceeds that in a well-nourished animal of the same weight as the undernourished one.

I suppose most of us only work with animals because of our interest in man, and I must make some mention of how our results on the weight of the brain may apply to man. Figure 2 shows the growth of the human brain compared with the growth of the body; as in the case of the rat, both values have been expressed as a percentage of a mature value, in this case the weight at eighteen years. These curves are

Figure 2. WEIGHT OF BRAIN AND BODY OF CHILD AS PER CENT OF VALUE AT 18 YEARS

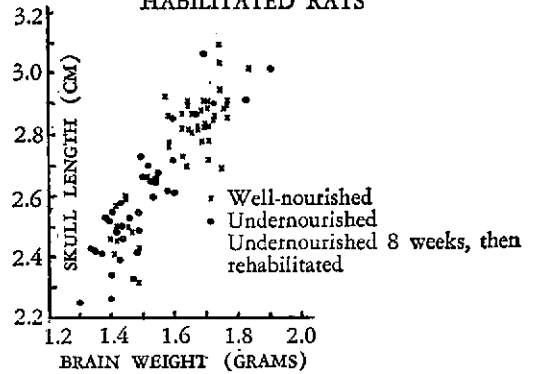


very like those for the rat—rapid growth of the brain during the first two years after birth, then a slowing down, and by the time the body is growing faster and faster the brain is growing quite slowly. Stoch and Smythe (1963) followed for two to seven years a group of children who were approximately half their expected weight at one year, and they postulated that if there is prolonged nutritional deficiency in the first year of life, when the brain is growing its fastest, the effect is likely to be more

profound and permanent than if the undernutrition comes later. I shall be coming to the effects of rehabilitation on the animals later, but so far as the weight of the brain during undernutrition is concerned, I think we can safely assume that the effect of undernutrition at any age will be to delay the growth of the brain less than that of the body, and by analogy with animals the younger the child when undernutrition begins the more the body will be held back relative to the brain.

There is one other point I should like to bring in here. A number of people are now measuring the head circumferences of malnourished children before and during rehabilitation because they are believed to give a good indication of brain size. We have made measurements of the skulls of rats of different ages and in different states of nutrition—well-nourished, undernourished, and in the process of rehabilitation after a period of undernutrition. Figure 3 shows the length of the skull plotted against the weight of the brain, and it is evident that the two measurements are related.

Figure 3. RELATION BETWEEN LENGTH OF SKULL AND WEIGHT OF BRAIN IN WELL-NOURISHED, UNDERNOURISHED, AND REHABILITATED RATS



Effect on the chemical structure of the brain

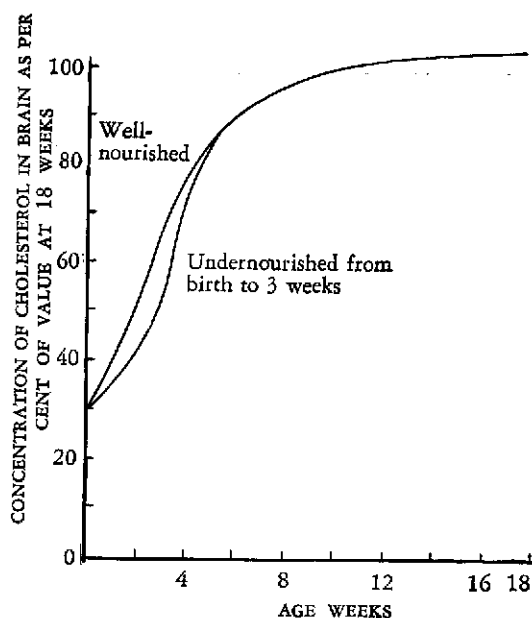
I have chosen cholesterol as a measure because it is one of the major solid constituents of the brain. It accumulates rapidly after birth, and once it has been incorporated into brain it seems to stay there and to take no part in

active metabolic turnover. It is not confined entirely to the myelin sheath, but that is where most of it is to be found, and we can therefore take the concentration of cholesterol in the brain as an index of the degree of structural development of the brain.

At birth the concentration of cholesterol in the rat's brain is about 30 per cent of the mature value. While the brain is growing rapidly in size during the first two weeks after birth, the concentration of cholesterol is also rising. If rats are undernourished from birth the deposition of cholesterol in the brain does not quite keep pace with the growth in size, and the brain that results has a slightly subnormal concentration of cholesterol (Figure 4; Dobbing, 1964). If undernutrition begins at three weeks of age, after the early rapid rate of growth of the brain has slowed down, the deposition of cholesterol more than keeps pace, and the concentration tends to be high rather than low (Table 4; Dobbing and Widdowson, 1965).

In pigs growing normally the concentration of cholesterol in the brain also rises as the brain grows. Phospholipid phosphorus rises along with cholesterol, whereas the concentration of DNA phosphorus falls, for as the degree of myelination increases the number of cells per unit weight of brain drops. The concentration of these constituents in the brains of the severely undernourished pigs changes dur-

Figure 4. CONCENTRATION OF CHOLESTEROL IN RAT'S BRAIN.



ing the year of undernutrition, in the same direction and indeed almost to the same extent as in a well-nourished littermate (Table 5; Dickerson, Dobbing, and McCance, 1965). Chemical development therefore goes on in the brain of the undernourished pigs even though their bodies remain so small. The development does not, however, go on equally in all parts

TABLE 4. Effect of Undernourishing Rats from 3 to 11 Weeks on Concentration and Total Amount of Cholesterol in Brain

	BODY WEIGHT (grams)	CHOLESTEROL	
		CONCENTRATION (g/100 g)	TOTAL IN BRAIN (milligrams)
Normally nourished, age 3 weeks	30	1.49	19.5
Normally nourished, age 4½ weeks	60	1.66	23.2
Undernourished age 11 weeks	60	1.98	28.1
Normally nourished, age 11 weeks	220	1.93	32.3

TABLE 5. Effect of Undernutrition on Development of Pig's Brain

	CHOLESTEROL (g per kg)	PHOSPHOLIPID P (m. moles per kg)	DNA-P (m. moles per kg)
Well-nourished pig weighing 5-6 kg, age 4 weeks	18.9	60.0	2.74
Well-nourished pig weighing 5-6 kg, age 1 year	27.5	72.6	1.79
Well-nourished pig weighing 150-200 kg, age 1 year	29.4	79.5	1.63

of the brain. Dickerson *et al.* (1965) have shown that in the cerebrum the deposition of cholesterol does not keep pace with growth in size, and the concentration after the year of undernutrition is lower than that in a well-nourished littermate. The cholesterol in the cerebrum of the pig, therefore, behaves as it does in the whole brain of rats undernourished from birth. In the cerebellum and basal ganglia the deposition of cholesterol more than keeps pace, and the concentration tends to be high rather than low, as it is in the whole brain of rats undernourished from the age of three weeks. I think the explanation is that the cerebellum and basal ganglia develop earlier than the cerebrum and are nearer their mature

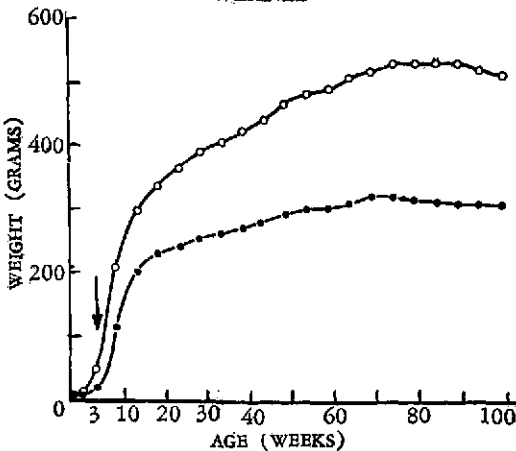
proportions when the undernutrition is imposed.

Effects of rehabilitation

In rats the ability to recover after a period of undernutrition depends on the age at which the undernutrition begins. If rats are made to grow slowly during the first three weeks of their lives by being suckled in large groups, they continue to grow slowly after weaning and do not catch up in body weight even if they have an unlimited supply of food thereafter; they become small adults (Figure 5; Widdowson and Kennedy, 1962). Their brains, which were large for the size of the body during the period of undernutrition, gradually acquire the right proportions for the body, but both body and brain are smaller than in animals that were never undernourished. The concentration of cholesterol in the brain, which was low during the first weeks of life, becomes normal (Dobbing, 1964).

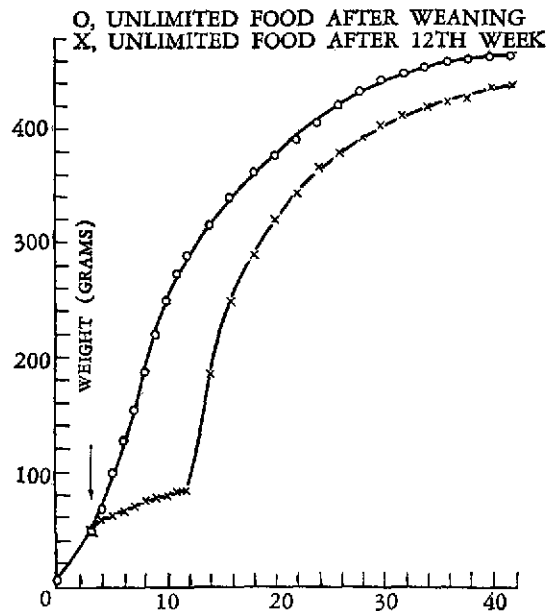
If rats are undernourished later, from the end of the third to the eleventh week of life, and are then rehabilitated, they at once begin to eat a great deal and to grow very fast (Figure 6; Widdowson and McCance, 1963). After a time the rate of growth slows down, before the mean weight has quite reached that of their well-nourished littermates. Their brains grow too, almost to the size they would have attained had the animals never been undernourished (Table 6); the concentration of cho-

Figure 5. BODY WEIGHTS OF RATS SUCKLED IN SMALL (o) AND LARGE (●) LITTERS WEANED



lesterol, which was normal during undernutrition, is maintained at a normal level (Dobbing and Widdowson, 1965). Cholesterol is deposited in the brain at the same rate as the growth of the brain in size—and this is very interesting, because adult brain has been said not to be able to synthesize significant amounts of cholesterol. Even more striking are the results on the undernourished pigs. These animals at one year are still the weight of a suckling pig, although they are past the age at which a normal female has produced a litter. When they are given unlimited food they also grow very fast; they may double their weight in ten days or so and treble it in three weeks. The rehabilitated animals do not grow quite so big as pigs that have never been undernourished, but they very nearly do (McCance and Widdowson, 1962; Widdowson, 1964). Their brains grow too and, as in the rats, come to form a perfectly normal proportion of the body weight (Table 7). The brain of the undernourished pig one year old has the capacity to synthesize enough myelin constituents almost to double the amount of cholesterol in it (Dickerson *et al.*, 1965). The capacity for reawakening biosynthetic processes in the brain, which have been held back by severe undernutrition, may have significance for malnutrition in early childhood, and perhaps—

Figure 6. EFFECT OF UNDERNUTRITION FROM 3RD TO 12TH WEEK OF LIFE ON GROWTH OF RATS SUCKLED IN SMALL GROUPS. ARROW SHOWS WEANING.



who knows?—even for regeneration of myelin in the central nervous system.

Effect of nutritional deprivation on the function of the brain

It must be confessed that we do not yet

TABLE 6. Rats: Final Effects of Rehabilitation on Body Weight and Brain Weight After Undernutrition from 3 to 11 Weeks

	BODY WEIGHT (grams)	BRAIN WEIGHT (grams)	BRAIN WEIGHT IN RELATION TO BODY WEIGHT (per cent)
Normally nourished, age 11 weeks	220	1.70	0.8
Undernourished, 3-11 weeks	60	1.45	2.4
Normally nourished, age 19 weeks	260	1.74	0.7
Undernourished, 3-11 weeks, and rehabilitated, 11-19 weeks	250	1.71	0.7

TABLE 7. Pigs: Final Effects of Rehabilitation on Body Weight and Brain Weight After Undernutrition for 1 Year

	BODY WEIGHT (kilograms)	BRAIN WEIGHT (grams)	BRAIN WEIGHT IN RELATION TO BODY WEIGHT (per cent)
Normally nourished, age 1 year	156	111	0.07
Undernourished, age 1 year	5.4	75	1.4
Normally nourished, age 3 years	250	140	0.06
Undernourished, 1 year, and rehabilitated, 2 years	200	125	0.06

know whether there is any relation between size or chemical composition and the function of the brain. We have studied the behavior of rats undernourished during the suckling period, and we have found that they are less active and inquisitive after weaning than well-nourished animals of the same age (Lat, Widdowson, and McCance, 1960), but the difference between them may be a matter of physical development, for if fast-growing and slow-growing rats of the same size are compared their activities are approximately the same. Nervous activity is undoubtedly influenced by sexual development, and in the rat this is much more closely related to body size than to chronological age.

All the results to which reference has been made so far have been obtained in animals suffering primarily from a deficiency of calories. We are now making studies of rats and pigs suffering primarily from a deficiency of protein. The detailed results on the brains, their weights and chemical composition, are not yet ready to present; in six months or a year I hope they will be. In the meantime I may say that we have noticed differences in the behavior of the animals suffering from the two types of deficiency. There is no doubt that undernourished rats and pigs are always ravenously hungry and ready to eat; if food

is offered to them they devour it at once. The protein-deficient animals appear hungry too—they come forward as soon as they hear the rattle of the food pots—but when food is offered to them they have no appetite and it is difficult to induce them to take any. Even during the early stages of rehabilitation, when they are offered a first-class diet, they do not go for it as the undernourished animals do, and they eat much less of it in the early stages. The protein-deficient animals are more docile, less easily disturbed. The rats are easy to handle, and the pigs pay little attention when someone comes near the pen. The undernourished rats are more vicious and inclined to bite when they are handled, and they appear more nervous in a strange situation. We are making quantitative measurements of various aspects of this different behavior.

Undernourished pigs have subnormal body temperatures and, even when the environmental temperature is kept high, spend most of their time huddled together in an attempt to keep warm. Protein-deficient pigs have normal body temperature and generally lie singly. Their skin seems to be itchy, even if it harbors no parasites, and they spend a considerable amount of their time scratching it.

When the undernourished animals are re-

habilitated they appear to become normal in behavior. Up till now we have made no detailed study of this, but we intend to do so in the near future.

Professor Platt and his colleagues at the National Institute for Medical Research have made histological studies of the central nervous system in pigs suffering from protein deficiency. They found striking changes, particularly in the spinal cord (Platt, 1962). They have also made EEG measurements, and one of the abnormalities described was a decrease of fast components in comparison with animals of the same age normally fed (Platt, Pampiglione, and Stewart, 1965). All these results are very suggestive and will no doubt be followed up. The workers observed that four weeks' rehabilitation on a good diet made a great difference to the behavior of the animals, and the EEG returned toward normal. The clinical improvement seemed to be more rapid than that of the EEG.

I should like to make one final point. Severely undernourished or protein-deficient animals cannot reproduce, for they do not become sexually mature until they are rehabilitated, but there is some evidence from animal experiments that less-severe protein deficiency of the mother may give rise to neurological and behavioral abnormalities in the young. Platt (1962) observed tremor and clumsiness in puppies born of mildly protein-deficient bitches; Cowley and Griesel (1959) found that rats that were born of mildly protein-deficient mothers and were themselves reared on the same sort of diet showed poorer learning ability than well-nourished controls. This opens up new possibilities for all of us, and it is clearly an aspect of nutritional deprivation that may have important implications for the psychobiological development of man.

Waterlow: Anyone who has done autopsies on malnourished children in underdeveloped countries is well aware of the relatively large size of the brain. This alone can have very important consequences. For example, in our work in Jamaica we have found that an under-

nourished child tends, rather surprisingly, to have a high total oxygen uptake per kilogram of body weight. One of the possible explanations is that a child who is half his normal weight has twice the normal proportion of brain, and it is not compatible with life that the oxygen uptake of the brain should be much reduced. This is an example of the fact that distortion in the pattern of the body can affect a great many of our determinations and the interpretation of them.

I should like to add one more point to what Dr. Widdowson has said. In our work with rats made protein-deficient after weaning, the brains were of normal size. When labeled amino acids were given, the total uptake in the brain, which I think in these experiments can be interpreted as a measure of the rate of protein synthesis, seems to be exactly the same, regardless of the nutritional state and body weight of the animal. It is as if the brain simply went on doing what it had to do regardless of the rest of the body around it, in much the same way as with oxygen and probably with glucose.

Roche: I wonder whether anyone has tried to find out the effect of force-feeding on the rats' brains; in other words, can one get larger brains or smaller brains in relation to the body size in force-fed animals?

I have another question, which is unrelated: what is the hemoglobin situation in these protein-deficient pigs? Do they have anemias, and, if so, of what type?

Widdowson: I am aware of Dr. Montgomery's work on the metabolic rate of protein-deficient children and the suggestion about the brain's accounting for their high metabolic rates. I am very much interested in what Dr. Waterlow said about the uptake of amino acids being the same in undernourished as in well-nourished animals.

We have force-fed rats with a low-protein diet, and after six weeks these animals weighed twice as much as rats that had the same low-protein diet but were not force-fed. The absolute weight of the brain was slightly lower

in the force-fed animals, so it formed a much smaller percentage of their body weight.

Roche: Do you know the approximate iron intake of the protein-deficient animals? Is it normal?

Widdowson: It is not inadequate. I think the protein rather than iron is the limiting factor. Iron was included in the mineral mixture added to their diet. I can't tell you exactly how much they had.

Roche: I have the impression that experimentally it has been very difficult to produce microcytic or iron-deficiency types of anemias with protein deficiencies.

Widdowson: This is a preliminary study. We are only just beginning our work on protein deficiency. In the calorie-deficient animals there is no anemia at all.

Paterson:* Have you any comment to make, Dr. Widdowson, on the general health of the animals?

Widdowson: In the undernourished pigs the big problem, as I have said, is to keep them warm. It is cold that kills them every time. Our biggest source of loss with the protein-deficient pigs is diarrhea; they can maintain their temperatures all right.

Dubos: I have had the privilege of being conditioned by Dr. Behar and his colleagues of the INCAP laboratory, and also of having been familiar with Dr. Widdowson's work. For the past year or two we too have tried to develop laboratory models that would to some extent duplicate some of the conditions that have been observed at INCAP. We have attempted to create not undernutrition, not caloric undernutrition, not even protein undernutrition, but rather protein malnutrition, using diets in which the source of protein was corn products or wheat gluten.

What we have observed is very similar to what Dr. Widdowson has reported: that a very short period of protein malnutrition—two to

three weeks—will have effects so lasting that they will persist throughout the whole life span of the animal, even if it is then placed on an optimum diet. In principle the experiment is as follows: At the time the animals are born, the mother is placed on a diet in which the only deficiency is that it is low in lysine and low in threonine. If she is kept on this diet for two or three weeks, until weaning, the young will never catch up with what would be expected of their chronological age, even if they are fed an optimum diet from the time of weaning on.

I have singled out lysine and threonine because we have now established that supplementing the deficient diet with these amino acids will correct the effects. In fact, it appears that threonine may be the most important of the deficiencies, rather than lysine, as we had expected.

We noticed your mentioning at the end of one of your papers, Dr. Widdowson, that you had observed a high rate of respiratory infections in malnourished animals. Being by profession concerned with infectious disease, and especially being conditioned by what has been observed at the INCAP laboratory, we have attempted to see whether a synergistic effect exists between infection and protein malnutrition. The animals are given as much food as they want, but the diet contains only about half as much lysine and threonine as an optimum diet would.

We have confirmed what was to be expected: that such animals are more susceptible to almost any type of infection than well-fed animals. What was more surprising, and unexpected, was that when the animals were maintained throughout on an optimum diet but were exposed at the time of birth to infection—by enteropathogenic coli or almost any ordinary bacterial species—they never recovered from it completely in terms of growth rates. In brief, exposing the animal at the time of birth to a few thousand enteropathogenic coli or other bacteria causes an infectious process that the animal overcomes but that

* Dr. J. C. S. Paterson, Director, Division of Hygiene and Tropical Medicine, Tulane University Medical School.

leads to its being 10 to 20 per cent underweight as compared with an animal that has not been similarly exposed.

All this indicates that events during very early life can so imprint (if I dare use this word) the organism that it can never correct for it. Lesions of very different natures, such as caloric malnutrition, amino acid deficiency, infectious processes, can have this effect. It is most likely when they all occur together that the result is those dramatic conditions that have been so well described from the different laboratories of Central America.

Behar:* Have you any information, Dr. Dubos, about the food consumption of the mothers that are placed on the protein diet you describe? I ask so that we can be sure there is not a restriction in the calorie intake as well.

Secondly, has an attempt been made, when these same mothers are lactating, to measure both the amount and the composition of the milk secreted? This question has been in our minds for many years and is extremely difficult to solve in human beings; which is affected more, the amount of milk secreted by the mothers or the composition of the milk? If it is the amount, the final result will be just what Dr. Widdowson was showing us in terms of caloric undernutrition, and not a specific amino acid deficiency.

Dubos: I can answer the first question. When the lactating mothers are fed a synthetic diet somewhat deficient only in lysine and threonine—half the optimum concentration—the food intake is enormous. If anything, the animals eat more than normal animals.

As to the composition of the milk, I have no knowledge.

Widdowson: Dr. Dubos reminds me of an observation from our own work. It is perfectly true that the rats that were undernourished from birth and were then, after weaning, put

onto unlimited food, but continued to grow slowly, did suffer much more from respiratory infections than those that were growing rapidly. A great many more died in the first year of life.

Thompson: I should like to ask Dr. Widdowson about her technique of undernourishment, which involved varying litter size—that is, having large litters and small litters. Does she concern herself with another variable involved—crowding? This as well as undernourishment could affect growth; the effect might be either additive or antagonistic.

Widdowson: Crowding may be important, but I don't think so. I think that the essential thing is to put more young rats with the mother than she has teats. If you put ten with her they can get a teat each and the effect on growth is much less than if you give her fifteen or twenty.

Thompson: On the basis of quite a lot of work on the effects of early stimulation, some of which I shall discuss this afternoon, I can conceive of crowding as being very significant. Mere numbers might produce quite different results, even if the nourishment was equal. There would be differences in temperature, in activity level, in degrees of competition, and so on. This is a variable that is difficult to control, but I think it needs to be taken into account.

Birch: I believe there is very good evidence about the effects of crowding on growth and behavior in a number of species, particularly rodents—studies both in the field, where the effects are profound, and in laboratory situations. I can suggest a simple and obvious strategy as a control for crowding. One can reduce the number of teats as well as increase the number of rats. If teats were to be excised, leaving only one, and then three rats were placed with one teat and another three rats with ten, the proportions would then be modified similarly.

Chagas: I have recently heard of the results of an experiment conducted by Bernard Halpern, which bears on Dr. Thompson's point

* Dr. Moisés Béhar, Director, Institute of Nutrition of Central America and Panama.

about crowding. The experiment indicates that the effect of certain psychopharmacological drugs is greatly altered when they are given to groups of animals kept together in the same cage; the toxicity level comes down very sharply. Only about half the amount other-

wise needed to produce a given effect will then be sufficient to provoke it.

Moderator: We turn now from animals to man, in our examination of nutritional deprivation. Dr. Joaquín Cravioto of the Children's Hospital, Mexico City.

NUTRITIONAL DEPRIVATION AND PSYCHOBIOLOGICAL DEVELOPMENT IN CHILDREN

Joaquín Cravioto

Scope of the Problem of Malnutrition in Preschool Children

Almost fifty years have elapsed since Correa in Yucatan, Mexico, described under the name *culebrilla* a pathological condition present mainly in toddlers and associated with a deficient intake of foodstuffs of animal origin. Reports from South America, India, Africa south of the Sahara, the Balkans, China, Southeast Asia, the Philippines, and Central America between 1908 and 1952 showed the widespread occurrence of the disease (Correa, 1908; Waterlow, Cravioto, and Stephen, 1960). The prevalence surveys of Brock and Autret (1952) in Africa, Autret and Behar (1954) in Central America, and Waterlow and Vergara (1956) in Brazil made apparent the great magnitude of the problem, confirming previous reports on the frequency of cases admitted to general and pediatric hospitals. Since 1955, protein-calorie malnutrition has been recognized as a disease of world-wide incidence; though it may vary in cause, it has basically the same characteristics of clinical and biochemical pathology in all countries and with regional variations of only secondary importance (Waterlow and Scrimshaw, 1957).

A number of reviews of protein-calorie malnutrition have appeared during the past fifteen years. Particularly detailed have been those of

Waterlow (1948) in the West Indies, Meneghelli (1949) in Chile, Brock and Autret (1952) in Africa, Oomen (1953) in Indonesia, Gopalan and Ramalingaswami (1955) in India, Gómez *et al.* (1953) in Mexico, Trowell, Davies, and Dean (1954), Behar *et al.* (1958), Ramos and Cravioto (1958), Waterlow, Cravioto, and Stephen (1960), and Viteri *et al.* (1964).

Prevalence and Incidence

There are no reliable statistics on the incidence of protein-calorie malnutrition. Hospital statistics are of little value for the purpose. In some regions 50 per cent of all children admitted to the pediatric wards are said to be suffering from malnutrition of one degree or another. Hospital figures, however, can only show whether a disease is rare, common, or very common, since without knowing the size and composition of the population served by the hospital it is impossible to relate these figures to the population at risk.

Few field surveys have been done on a large enough scale to provide valid data. An exception was the survey of Rao *et al.* (1959) in India, in which more than four thousand children under five were examined in their homes. The prevalence of severe protein-calorie malnutrition accompanied by clinical edema was just under 1 per cent. Since the subjects were

examined only once, and since it is reasonable to assume that in a month's time a child with severe protein malnutrition either recovers or dies or is removed to a hospital for treatment, it is reasonable to estimate—if there is no seasonal variation—that some 10 per cent of the preschool children would develop severe protein deficiency in the course of the year.

Mortality

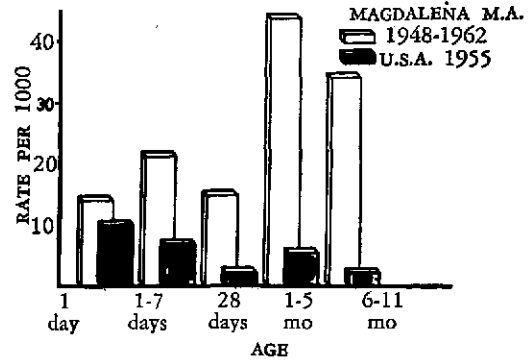
When the age-specific mortality rates for preschool children in the U.S.A. are compared to those in areas where protein-calorie malnutrition is prevalent—for example, the rural areas of Guatemala—it is readily apparent that starting with figures almost equal for deaths occurring during the first day of life, the U.S. rates decline rapidly in contrast to the Guatemalan figures. This phenomenon is even more striking when the comparison is expressed as a ratio (see Table 1, Figure 1) (Béhar, *et al.*, 1963).

TABLE 1. Mortality Rates for Preschool Children of Rural Guatemala and the United States, By Age

AGE GROUP	RATE PER 1,000		RATIO (GUATE- MALA/ U.S.)
	MAGDA- LENA (GUATE- MALA)	UNITED STATES	
less than 1 day	13.8	10.0	1.3
1 to 7 days	21.3	7.0	3.0
7 to 28 days	14.9	2.1	7.0
28 days to 1 year	77.8	7.3	10.6
1 to 4 years	29.5	1.1	26.8

In the United States the rate decreases rapidly after birth, as soon as perinatal causes cease to be the main determinants; after the first month of life, and more so after the first year, the chances of a preschool death are rather small. In rural Guatemala, on the other hand, as in most preindustrial countries, survivors of the perinatal period are still quite likely to die during the first year of their lives and con-

Figure 1. AGE-SPECIFIC MORTALITY DURING FIRST YEAR OF LIFE IN GUATEMALA AND UNITED STATES



tinue at great risk for another two or three years.

An investigation on causes of death after the perinatal period shows that respiratory and gastrointestinal disorders, together with intestinal parasites, are those reported most frequently in the official records. Very seldom are deaths registered as due to any form of malnutrition. Evidence indicates that this is largely an artifact of registration practice. Béhar, through an investigation of each death occurring over a period of two years in four rural Guatemalan villages where the mortality rates are similar to those for the country as a whole, found that out of 109 deaths occurring in children under five, 38 were typical cases of severe protein-calorie malnutrition accompanied by edema (kwashiorkor), and 2 were of severe malnutrition without edema. In other words, approximately 33 per cent of all deaths in this age group were undoubtedly related to malnutrition. If to this figure are added all the other cases in which malnutrition was an important contributory factor although not the immediate cause of death, it could be easily concluded that malnutrition played a major role in no less than 50 per cent of the total number of deaths in preschool children (Béhar, Ascoli, and Scrimshaw, 1958).

At present it is an accepted fact that deaths due to malnutrition are customarily listed under other causes and that official statistics fail to reveal protein malnutrition as a main con-

tributor to the high rates of preschool mortality. The reason is that in the vast majority of regions where malnutrition is prevalent there is little or no medical certification of death and only rarely can the layman in charge of the civil register make a diagnosis of malnutrition. Moreover, since a large number of malnourished children die of acute electrolyte disturbances due to diarrhea (Gómez *et al.*, 1956) or of respiratory infections, many deaths from malnutrition are officially entered, even in places with medical certification, as caused by infectious diarrhea and/or bronchopneumonia.

Because of inadequate sanitary conditions, children living in preindustrial regions tend to suffer more from enteric infections and other communicable diseases, but it is also important to consider that the severity of the consequences has been shown to be due in part to the almost universal presence of malnutrition of various degrees. Thus, Gordon *et al.* (1964) have reported that in a rural area of Guatemala between February 1961 to June 1962, the percentage of cases of severe diarrhea came to 22.9 among well-nourished children but 40 among third-degree-malnourished subjects. Similarly, Vega *et al.* (1964), studying a measles epidemic, found that the frequency and severity of bacterial complications increased in proportion to the intensity of malnutrition in children below the age of five.

Separately or in combination, infection and malnutrition as important causes of death have been disappearing in highly industrialized countries, but in the preindustrial areas of the world they continue to be responsible for the largest proportion of total deaths (Cravioto, Vega, and Urrutia, 1964).

Morbidity

It is important to recognize that at present more children survive severe protein malnutrition than die of it. Better knowledge of the biochemical characteristics of malnourished children, together with better means for rapid diagnosis and assessment of the effect of treatment of electrolyte disturbances and infections,

has played a major role in this reduction. The increasing number of survivors is reflected in the fact that whereas in 1952 approximately 30 per cent of children with third-degree malnutrition died, fewer than 5 percent died during 1962-1964. Thus, at present the great majority of children with protein-calorie malnutrition do not die, but yield a pool of survivors who may be handicapped in a variety of ways and for varying periods of time, transiently or permanently.

When malnourished children start to recover they do so with great rapidity at first. They very often grow at twice or three times the normal rate for their chronological age. However, if observations are continued for a longer period it becomes apparent that the initial rate is not excessive but is equal to that seen in a normal younger child of the same size as the malnourished subject; later on the rate shows the periodic accelerations and decelerations of normal growth but with a time lag in comparison with the child who has not suffered early malnutrition. Therefore, the weight gain is size-dependent and not age-based.

Pediatricians and nutritionists have often been misled by the high rates of growth at the beginning of the rehabilitation period. They have speculated that it will continue until the child catches up to normal children. Unfortunately, the few studies available indicate that puberty appears and growth ceases at the usual chronological age, with the net result being an undersized adult. At adolescence children from areas where infantile malnutrition is prevalent are shorter than children from the same age and ethnic group in more developed areas (Aguilar, 1944; Ramos Galván *et al.*, 1958; Scrimshaw *et al.*, 1955; Meredith, 1951; György, 1960; Cravioto, 1963).

Dean's studies on body weight and measure of rehabilitated cases show that after the child has recovered his length remains shorter and his skeletal development retarded in comparison to that of normal individuals of the same age and ethnic group (Dean, 1960). Similar

findings have been reported by Barrera Moncada (1963), who has followed Venezuelan children recovered from malnutrition for periods up to ten years.

The effect of previous malnutrition on the ultimate proportions of body segments is illustrated by the data of Leitch (1951), whose analysis of the Carnegie-United Kingdom Dietary and Clinical Survey showed that leg length was a better indicator of expenditure on food, an indirect way of assessing nutritional status, than body height. Ramos Galván (1964) has reported that ratios of body proportions in school children living in conditions that produced chronic malnutrition in early infancy might be a better way of assessing adequacy of intake than total height or weight.

Numerous examples of physiological and biochemical alterations in malnourished children show that malnutrition not only arrests certain aspects of biochemical maturation but also seems capable of producing a reversion to an earlier stage of development. Thus, for example, when water content and distribution in malnourished children are recalculated on the basis of the age indicated by the actual weight or height, it is apparent that both content and distribution are "normal" for a child who would have the same height or weight as the pathological patient (Cravioto, 1962). Similar conclusions can be reached when the data for fat absorption, plasma lipid concentrations, changes in proportions of alfa and beta lipoproteins, modifications of cholesterol concentrations in blood, and urinary excretions of creatinine are plotted against the age for height and/or the age for weight (Cravioto, De la Peña, and Burgos, 1959).

Immunologically too, it is of interest that when challenged antigenically children recovering from malnutrition give responses similar in magnitude to those obtained in normal infants very much younger (Olarre, Cravioto, and Campos, 1956).

Kumate *et al.* (1964) found in 118 malnourished children a diminution of about 20 per cent in the levels of hemolytic complement.

The decreases were similar for all four components determined: C-1, C-2, C-3, and C-4. The correlation between the degree of malnutrition, estimated as the percentage of difference between the theoretical and the actual body weight, although low, was statistically significant. Similar results were obtained by Ramunni and Moretti (1960) and by Vasile (1929).

Unpublished observations of Kumate at the Children's Hospital of Mexico have shown that 7-S gamma-2-globulin is reduced in severe malnutrition, with average values of about 400 mg per cent as against about 1,000 mg per cent in well-nourished controls.

Free amino acid concentrations in blood plasma of children affected with either marasmus or kwashiorkor generally show an abnormally high ratio of phenylalanine to tyrosine (Cravioto *et al.*, 1959). A similar finding in urine previously reported by Cheung *et al.* (1955) suggests the possibility of a defect in the enzyme system that metabolizes phenylalanine into tyrosine.

The extent to which normal biochemical maturation can be altered in humans by malnutrition is perhaps best illustrated by Dean, who has been able to reproduce in preschool malnourished children the main biochemical lesions characteristic of the absence or a marked reduction of certain enzymes participating in the metabolism of the aromatic amino acids histidine, tyrosine and phenylalanine—a phenomenon normally present only in the newborn infant (Dean and Whitehead, 1963).

Studies on morbidity thus show that previously malnourished children are stunted in growth, exhibit physiological derangement, and are delayed in some aspects of their biochemical maturation.

Psychobiological development

In spite of these impressive advances made in the knowledge of the clinical and biochemical aspects of nutrition deprivation during the past seventeen years, scientists have only recently become concerned about the potential delay in the psychobiological development of

infants suffering from protein-calorie malnutrition.

The little attention given to this subject matter is quite surprising in view of the fact that from the very first descriptions of protein-calorie malnutrition in children it was clearly stated that disturbed behavior was among the earliest symptoms, that it prevailed throughout the duration of the disease, and that a return to normal behavior could be considered one of the best guides for prognosis. The accounts given by several authors showed that apathy was probably the single most common finding; the severely ill patients seemed to have lost all the normal curiosity and desire for exploration so characteristic of the normal child. Renewal of interest is still considered one of the most reliable signs of improvement (Trowell, 1937; Clark, 1951; Gómez *et al.*, 1954; Valenzuela, Hernández Peniche, and Macías, 1959).

Following Wilson's attempt to distinguish different categories of apathy—primarily physiological, "apathy" at the community level, and "apathy" as a characteristic of a regional culture (Wilson, 1964)—the apathy of the protein-calorie-deficient child would possibly be a mixed type: deprivation itself could cause it, as is the case in experimental animals fed on low-protein, high-carbohydrate diets (Platt, Heard, and Stewart, 1964), and on the other hand it could also be elicited as a sequela to the emotional deprivation and loss produced by the separation that accompanies hospitalization.

It has been repeatedly stated that in most communities where malnutrition is highly prevalent the mother-child relationship prior to weaning is a very close one, to the point that the mother takes the nursling with her everywhere she goes. In conjunction with the observations of Geber and Dean (1956) that recovery is more rapid among infants whose mothers show the greatest interest and solicitude, this fact has been interpreted as suggesting that separation anxiety may play an important role in the behavioral disturbance. In addition, the psychological behavior of malnourished infants is markedly similar to that of healthy children

fifteen to thirty months old who have been separated from their mothers by hospitalization, as described by Bowlby (1960). Deprivation of an effective and continuing mother-surrogate—for example, by repeated, random changes in responsibility for the child's care—may also play a part in some communities, where this is a common practice starting when the mother's next pregnancy becomes evident (Cravioto, in preparation). However, it is important to remember that, as Meneghello (1949) has pointed out, the psychological changes in malnutrition are not simply a response to hospitalization, since they are already present.

No matter what the cause of the apathy, it is clear that as chronic malnutrition develops from mild-moderate to severe, failure to respond appropriately to changing stimuli is reflected in progressive behavioral regression.

Since behavioral changes, though less dramatic than physical wasting, may have a greater importance and in the long run be more important because of their possible interference with cognitive development, research from areas in which protein-calorie malnutrition in children is widespread has tried first of all to answer the practical question of whether the resulting biochemical and growth lags are associated with slowness in mental development. Investigators from these areas have also wished to know whether such lags, when found, are permanent or merely transient.

Three strategies have been used to assess the potential relationship between nutritional deprivation and the functioning of the central nervous system: electroencephalography, psychological test behavior, and evaluation of development of brain functioning.

Electroencephalographic Studies

Electroencephalography as a method for studying neural functions in malnourished infants has been employed by Sarrouy (Sarrouy, Saint-Jean, and Clause, 1953), Engel (1956), Valenzuela (Valenzuela, Hernández Peniche, and Macías, 1959), and Nelson and Dean (1959). The EEG recordings have consistently

shown changes in the form, frequency, and amplitude of the waves, even in mild-moderate cases. On admission all the patients exhibit either polyrhythmic or monorhythmic and sinusoidal waves. The frequency is considerably diminished; the amplitude, also markedly reduced, attains values of only 30 to 50 microvolts instead of the 150 to 200 characteristic of waves of such a low frequency. Using chloral hydrate sedation, Valenzuela found an absence of the rapid rhythm normally shown by healthy infants under sedation. With successful treatment the EEG tends more and more to conform to that of healthy children of similar age. First the frequency and amplitude of the waves increases, although bouts of slow monorhythmic waves appear from time to time. Finally, when the child is well on the way to recovery, the abnormalities disappear; the total rehabilitation takes from forty to sixty days.

In 5 out of 47 patients studied, Nelson and Dean found focal disturbances in the temporal areas of the brain. These have been interpreted as indicative of a local reaction to the generalized state of intracellular overhydration that is a very common feature of severe chronic infantile malnutrition (Frenk *et al.*, 1957). Their usual origin in the temporal lobe may be only a reflection of the lobe's tendency to react more easily than other brain regions.

Psychological Test Behavior

1. Mild-moderate forms of malnutrition

Kugelmass, Poull, and Samuel (1944) studied the effects of nutritional improvement on mental performance in children matched for chronological age and IQ but differing in nutritional status. Two matched groups each containing 50 children ranging in age from two to nine years were established. One was identified as normal well-nourished, the other as normal malnourished. After a period varying from one to three and a half years, during which the nutritional status of the normal malnourished group was improved, the psychological testing was repeated. Whereas the average IQ of the

initially well-nourished group remained markedly stable, that of the initially malnourished group rose an average of 18 points following improvement in nutritional status.

Stoch and Smythe (1963) in South Africa have followed semilongitudinally two groups each composed of 18 Negro children ten months to two years old and 3 between two and three years. At the beginning of the study none of the children showed evidence of organic disease apart from gastroenteritis that responded rapidly to treatment. The essential difference between the two groups was in their state of nutrition, as judged by anthropometric measurements.

The group considered better-nourished included children attending an all-day nursery, where they received adequate meals and vitamin supplements, while both parents worked. The undernourished children were seen for the first time at the age of about one year and were subsequently examined at six- to twelve-month intervals. Although the families of the better-nourished group tended to be larger and to have higher incomes, less unemployment, and slightly better educations, both groups were considered to belong to the lowest economic stratum of unskilled labor. The intelligence quotients of the parents in both groups were very low. The raw scores on the Raven test were not significantly different.

The children were tested by means of the Gesell Infant Scales of Mental Development up to the age of two years; with the Merrill-Palmer test, adapted to African children, from two to six; and thereafter with the Individual Scale of the National Bureau of Educational Research of South Africa, which is based on the 1916 Stanford-Binet Scale. Anthropometric measurements were also taken every time the children were examined.

The results showed that at all ages not only were the figures for height, weight, and head circumference lower for the undernourished group, but the mean intelligence quotient was also well below that of the better-nourished group. The disparity remained relatively con-

stant throughout the observation period. A difference of 22.62 points found on the final testing was statistically significant at the 1 per cent level.

Cross-sectional studies of behavioral development conducted in Africa (Geber and Dean, 1957a), Mexico (Cravioto and Robles, 1962), and Guatemala (Wug de León, de Licardie, and Cravioto, 1964), using the Gesell technique and the André-Thomas method, show that in these preindustrial countries newborn infants generally score higher, and never lower, on psychomotor and adaptive development than North American or European children. The Gesell tests, usually considered suitable only for children over four weeks of age, can be used with younger African, Mexican, and Guatemalan children because their motor development at two or three weeks is similar to that of Western European infants twice or three times as old. Interestingly enough, Nelson and Dean (1959) have reported that electroencephalograms of newborn African infants are suggestive of greater maturity than is usually found in the newborn European child. Soon after birth, however, children from these preindustrial areas show deceleration, so that by the time they are eighteen to twenty-four months old their performance is below that shown by their European counterparts.

Following Dean's idea of expressing the Gesell Developmental Quotients (Y) for a given age (x) on the basis of a scale on which

100 represents the performance of the "normal" North American or European child of the same age as the children being tested, the relationship between quotients and chronological age could be described by a curve of the type $Y = ax - b$ for the total span of 0 to 42 months; a satisfactory approximation of this curve would be obtained by fitting a series of straight lines over subsets of smaller age intervals (Tables 2 and 3).

Even children who later develop kwashiorkor usually grow well during the first months of life. Later on, when the mother's milk no longer meets the infant's needs and suitable supplements are not added, weight and height increments begin to diminish. By the time the child is completely weaned, which for most areas of Latin America usually is around the eighteenth to the twenty-fourth month, height is practically stationary and weight may even show a slight decrease.

In six different communities—two of typical mestizos, one of Zapotec Indians, one of Nahua Indians in Mexico, and two of Cakchiquel Indians in Guatemala—high correlations were found between deficits in height and weight and motor and adaptive developmental scores (Table 4). No statistically significant association could be demonstrated between mental scores and cash income, crop income, parental education, parental hygiene, or type of housing (Robles *et al.*, 1959; Espinosa Gaona, 1962;

TABLE 2. Calculated Values of a and b for Relation Between Percentage of Theoretical Behavior Determined by Gesell Test (Y) and Chronological Age in Months (x) Derived from Results in Pre-School-Age Groups in 2 Indian Villages, Guatemala (Empirical Equation of the Type $Y = a-bx$)

FIELD OF BEHAVIOR	AGE GROUP (months)					
	0-12		13-24		25-36	
	a	b	a	b	a	b
Motor	155.03	-5.22	128.18	-1.53	157.65	-1.89
Adaptive	122.69	-1.76	110.07	-0.53	130.45	-1.26
Language	131.51	-2.84	90.62	-0.07	147.02	-1.88
Personal-Social	110.68	-0.73	111.49	-0.60	143.35	-1.16

TABLE 3. Calculated Values of a and b for Relation Between Percentage of Theoretical Behavior Determined by Gesell Test (Y) and Chronological Age in Months (x), Derived from Results in Groups of Pre-School-Age Groups in Rural Mexican Village (Empirical Equation of the Type $Y = a \cdot bx$)

FIELD OF BEHAVIOR	AGE GROUP (months)					
	0-12		13-24		25-36	
	a	b	a	b	a	b
Motor	137	-2.61	124	1.36	77	+0.54
Adaptive	143	-3.77	116	-1.21	78	+0.35
Language	139	-3.29	116	-1.44	72	+0.39
Personal-Social	128	-2.09	114	-1.15	101	-0.32

Ramírez, 1960; Ramos Galván, Pérez Navarrete, and Cravioto, 1960)

Ramos Galván (1960), through a series of cross-sectional and longitudinal studies, has constructed provisional weight and height tables for age of normal Mexican children. When the actual weights and heights of rural Mexican children with mild-moderate protein-calorie malnutrition, expressed as a percentage of the provisional standard, were compared with performance scores on the Terman-Merrill test adapted to local conditions, a positive correlation was found. Better scores were associated with the smallest differences between theoretic

cal and actual weight and height. Further, when "age for height"—that is, the age of a normal child of the same height as the malnourished subject—was related to mental performance, a positive and highly significant correlation was found, suggesting a concurrent deceleration of somatic and mental growth (Cravioto, 1964).

2. Severe Protein-Calorie Malnutrition

Barrera Moncada has explored the psychological test behavior of severely malnourished children by means of the Gesell technique. Performance in all the fields of behavior tested gave lower developmental scores than the standard calculated for children of similar age and ethnic group. The better scores were in general motor development and the greatest retardation was in language. As a rule, older patients exhibited more marked deficits. Similar findings have been described for Africa (Geber and Dean, 1957b) and Mexico (Robles, Ramos Galván, and Cravioto, 1959).

Studies on the somatic growth of infants in Latin American communities with a high prevalence of malnutrition and infectious diseases have indicated that the weight curves during the first five years of life can be described in three well-defined phases. The first comprises a period of four to six months after birth. It is characterized by weight gains similar to those of normal children born in highly industrialized countries—a phenomenon most apparent when the gains are expressed as percentages of birth

TABLE 4. Values for Empirical Constants a and b Calculated for Relation Between Percentage of Theoretical Adaptive or Motor Behavior and Percentage of Mean Theoretical Weight for Age in Rural Children of Cakchiquel Language Group (Equations of the Form $Y = a \pm bx$ Where Y = % of Theoretical Behavior and x = % of Theoretical Weight for Age)

FIELD OF BEHAVIOR	STATISTICAL SIGNIFICANCE OF PREDICTION EQUATION		
	a	b	"F" Test
Motor	10.48	1.22	11.77*
Adaptive	65.92	0.42	5.79**

* Significant at 1% level

** Significant at 5% level

weight. The second phase extends from the sixth to approximately the thirtieth month. During this period weight gains are progressively lower, reaching their minimum between the eighteenth and the twenty-fourth month, after which they tend to rise steadily. The third phase marks an apparent return to values normal for the chronological age (Ramos Galván *et al.*, 1958).

In view of all this, and considering that it is during the period of maximal growth that malnutrition might most strongly influence the ultimate size and performance of the mature individual, Cravioto and Robles (1965) sought to assess the psychological test performance of severely malnourished children during at least three different age periods: below six months, between six and thirty months, and after thirty months.

From among the children admitted to the Nutrition Ward of the Children's Hospital of Mexico, all who were classed as suffering from third-degree protein-calorie malnutrition were considered suitable for the study. The definition of "third-degree" followed the criteria of Gómez *et al.* (1956) and the suggestion of José María Bengoa,* who includes in this group all malnourished children with pitting edema, regardless of their weight.

Immediately after any infectious and/or electrolyte disturbances had been corrected, the psychological test behavior of the children was explored by the Gesell method. The tests were repeated every two weeks during the entire time the children were in the hospital.

At the end of one year of study it was possible to analyze serial information obtained in 6 infants below six months of age, 9 children between fifteen and twenty-nine months, and 5 children between thirty-seven and forty-two months.

The results of the first test session confirmed once more the previous reports of lower scores in all fields of behavior. As the patients re-

covered from malnutrition, their developmental quotients increased in most cases and the gap between the theoretically normal and the actual performance progressively diminished, except in the group whose age on admission was below six months. These infants increased their mental age only by a figure equal to the number of months they remained in the hospital. In older children not all the fields of behavior explored with the Gesell technique recovered at the same speed. Language, which was in general the most affected, returned toward normal at the slowest rate.

When serial data for each child were plotted against days of hospitalization, the rate of recovery from the initial deficit was seen to vary in direct relation to chronological age at admission. The older the group, the steeper the slope (Table 5). The slopes are steep enough and progress in the first two weeks of treatment great enough that the difference between early and final test results are unlikely to be due solely to the extra care and attention that the children received in the hospital.

Of the factors that contribute to a child's intellectual development, among the most influential are considered to be the educational level of the parents, especially the mother, and her attitude to intellectual development. Knobloch and Pasamanick (1963) have shown that developmental quotients vary systematically according to the level of the mother's education and that this relation is progressively more manifest as the child grows older. Similar findings directly associating the child's and the parents' IQ have been reported by Kagan and Moss (1959).

Although the influence of these factors has not been qualified in the case of severely malnourished children, it is known that the parents of the great majority either are illiterate or have had very little schooling. In a study of the environment in which these children live, Martínez, Ramos Galván, and De la Fuente (1951) found a great number of mothers with low intelligence quotients. Furthermore, it is a recognized fact that children suffering from

* Nutrition adviser, WHO; personal communication.

TABLE 5. Regression Equations for Relation Between Psychological Test Behavior (Y) and Days of Successful Treatment (X) in Three Groups of Children Recovering from Severe Protein-Calorie Malnutrition

FIELD OF BEHAVIOR (DEVELOPMENTAL QUOTIENT IN MONTHS)	AGE GROUP (months)		
	3-6	15-29	37-41
Motor	2.18 + 0.03X	12 + 0.06X	14 + 0.10X
Adaptive	2.30 + 0.03X	12 + 0.08X	15 + 0.11X
Language	2.0 + 0.03X	9 + 0.05X	15 + 0.07X
Personal-Social	2.11 + 0.03X	10.5 + 0.07X	16 + 0.11X

protein-calorie malnutrition generally come from homes where economic pressure hinders the parents from giving adequate stimulation for development.

Stoch and Smythe (1957), in their semi-longitudinal study of mental development in Cape Town, South Africa, reported that parents from both well-nourished and undernourished children score very low on the Raven Test of Intelligence.

The diagnosis of subnormal mentality can seldom be established, even in severe cases, before sixteen weeks of age because the tests that can be used during this period of life bear a very low correlation with subsequent measurements of intelligence (Bayley, 1958). After sixteen weeks the prediction of intellectual potential is more reliable, especially in groups from whom a rich cultural environment is not expected.

Knobloch and Pasamanick, in summarizing the influence of certain variables on the prediction of later intelligence, come to the conclusion that it is necessary to abandon the generally accepted concept of the level of motor development as an index of future intellect, since accelerated motor behavior does not necessarily indicate a superior intellectual potential and children with serious mental defects may have a normal motor development. Therefore, though knowledge of the status of motor development is indispensable for a correct diagnosis of current behavior, it does not suffice by itself for an estimate of the future intellectual level. If intelligence is defined as mental

adjustment to new circumstances and is characterized by increasing complexity in the channels through which the subjects acts on objects, it can be seen that, as Knobloch and Pasamanick have suggested, the adaptive sphere explored by the Gesell method is precisely the area of behavior most analogous to later intelligence, since it is concerned with the organization of stimuli, the perception of interrelationships, and the separation of the whole into its component parts with subsequent resynthesis in a manner adequate to solve a new problem.

Taking into account all the previous considerations, the persistence of low performance scores during rehabilitation among the infants who suffered protein-calorie malnutrition before the age of six months seems to indicate a probable loss in intellectual potential. In older groups, it is possible that the initial deficit will completely disappear if other relevant factors do not interfere.

These proposals seem to be supported by the findings of Barrera Moncada (1963), who has reported normal IQ's in 20 rehabilitated cases, all of whom were over two years and ten months of age at the time of admission to the study, when tested two years after their discharge from the hospital. Similarly, Kugel-mass, Poull, and Samuel found, as has been said, that improvement in the diet of undernourished children over two years of age was followed by an improvement of 18 points in the IQ. The results obtained in adult volunteers by Keys *et al.* (1950) point in the same direction. As age advances the effects of

nutritional deprivation on the central nervous system tend to disappear more rapidly.

Evaluation of Development of Brain Functioning

To explore further the hypothesis that serious malnutrition of either primary or secondary causation during the preschool years interferes with the development of the central nervous system and lowers the adaptive capacity, Cravioto, Licardie, and Birch carried out a cross-sectional study of the total primary-school population of a rural Guatemalan village in which prior information indicated the presence of a significant amount of acute or prolonged malnutrition in preschool children. Malnutrition was defined retrospectively in the children ranging from six to eleven years.

The primary basis for such identification was significantly shorter stature than the rest of the children. With this procedure, two groups of the same ethnic background were identified, representing the upper and lower quartiles of the age groups studied. In order to account for inherited differences in height, anthropometric information was obtained on the fathers and mothers. Further, since no psychological capacity is immune to environmental influences, comparative information was obtained on the socioeconomic and educational status of the children's families.

In addition, the rural study was replicated on an upper-class urban sample of schoolchildren whose variations in height would be most unlikely to be related to nutritional deprivation.

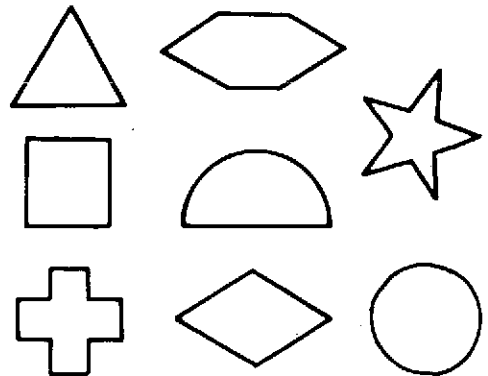
The behavioral function chosen for study was the development of intersensory organization, because its course is clearly defined and because this is a primary mechanism underlying more complex adaptive capacity. The specific method employed was that elaborated by Birch and Lefford (1964). These authors have shown that when studied by the technique of intersensory equivalence, the interrelations among three sense systems—touch, vision, and

kinesthesia—improve as a growth function with age.

Intersensory equivalence was evaluated in three sensory systems: vision, kinesthesia, and haptic touch. A haptic stimulus is one that is mediated through touch and active exploratory movement of the hand. The children were asked to judge whether two simultaneously presented stimuli were the same or different in shape: a form presented to one sensory system (standard) was compared with forms presented in another sensory system (variable). Thus, a visually presented standard was compared with a series of forms presented either haptically or kinesthetically. Similarly, a haptically presented standard was compared with a kinesthetically presented series. From such examination was determined the existence of cross-modality equivalences and nonequivalences between the visual and the kinesthetic, the visual and the haptic, and the haptic and kinesthetic sensory systems.

Eight blocks, selected from the Seguin Form Board, were used as the test stimuli for the visual and haptic modalities. As a visual stimulus, the block was placed on the table directly in front of the child. For haptic stimulation, the child actively explored with his hand a Seguin block placed behind an opaque screen, where he could not see it. Kinesthetic information was provided by the examiner's guiding the child's hand, again behind a screen out

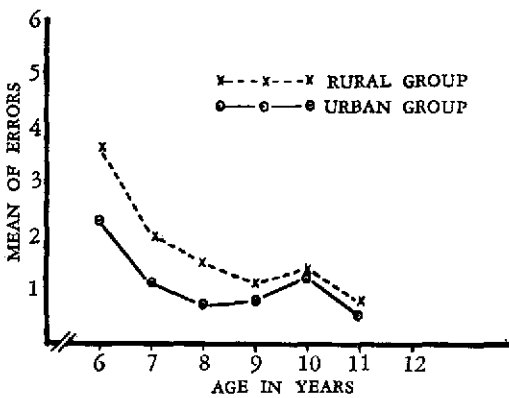
Figure 2. GEOMETRIC FORMS USED IN ALL PHASES OF STUDY



of his sight, through a path describing the geometric form. The patterns—the same in size and shape as the blocks used for visual and haptic stimulation—were cut one-eighth of an inch deep in four-by-six-inch linoleum blocks. The forms used are shown in Figure 2.

The results showed that each of the pairs of intersensory relations improved with age in both the rural and the upper-class urban groups. The error curves are almost identical in shape (see Figure 3), the only difference being that the urban children were significantly more advanced.

Figure 3. ERRORS OF NON-EQUIVALENCE, HAPTIC-KINESTHETIC, IDENTICAL FORMS

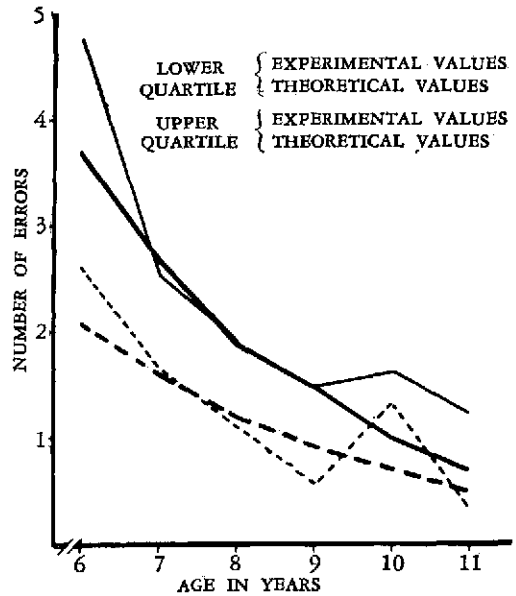


When the intersensory performances of children in the upper height quartile were contrasted with those in the lower quartile, it was only in the rural group that significant differences were manifested. This difference is illustrated by Figures 4 and 5, in which haptic-kinesthetic performances by age of the two height extremes are plotted.

The anthropometric information collected for the parents revealed that the height difference between the upper and the lower quartiles of the urban sample was mainly a reflection of family differences in stature. In the rural population, on the other hand, there was no significant association between the statures of parents and of children.

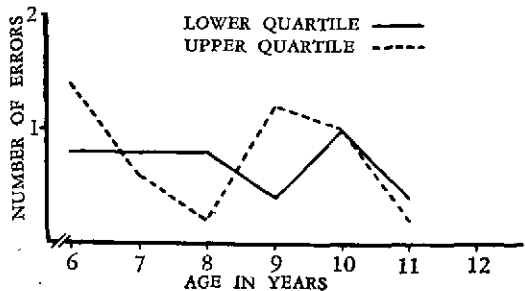
The lack of association between height and

Figure 4. RURAL GROUP: HAPTIC-KINESTHETIC MODALITIES, IDENTICAL FORMS



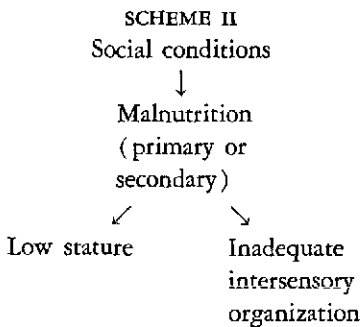
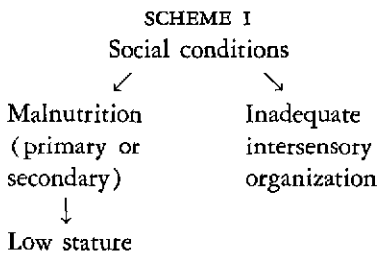
performance in the urban group has been interpreted as an indication that such a correlation exists only when the height difference reflects a different nutritional background—which could derive either from failure to have received appropriate amounts and kinds of food (primary malnutrition) or from repeated infectious episodes that have interfered with the child's nutritional status (secondary malnutrition). This interference could occur directly, through an increase in tissue protein catabolism

Figure 5. MEAN ERRORS FOR INTERSENSORY JUDGMENT OF NONIDENTICAL FORMS AT DIFFERENT AGES (URBAN GROUP), HAPTIC-KINESTHETIC



without a concomitant increase of protein intake (Wilson, Bressani, and Scrimshaw, 1961), or indirectly, through anorexia and through the social custom of reduced feeding, particularly for preschool children, during illness and convalescence (Cravioto, 1958).

A question arises whether the inadequacy in intersensory functioning found in the short children of the rural group is part of the picture of malnutrition or whether both intersensory inadequacy and poor growth are associated with underlying subcultural differences that may have contributed to each of them independently. In one case, that is, the immediately underlying process is viewed as malnutrition; in the other, social conditions lead directly to poor intersensory functioning. The two alternatives can most readily be analyzed if they are considered diagrammatically.



In Scheme I, malnutrition and intersensory inadequacy both derive from a background of social impoverishment. They bear no direct relation to each other but are indirectly associated by virtue of a common origin. In Scheme II, social conditions result in malnutrition,

which in turn lead to low stature and poor intersensory development.

Although it is impossible, on the basis of the available information, to accept or reject either hypothesis, certain inferences attaching to each can be explored. The main thrust of Scheme I is that social deprivation, including inadequate opportunities for learning, independently contributes to poor intersensory development. If this were correct both low stature and poor intersensory performance would be expected to show a significant association with a variety of social conditions that have been implicated as contributing to poor psychological growth. Of great importance, therefore, is the fact that the family data collected for the rural children revealed no association with financial status, with housing facilities, with proportion of total income spent on food, or with personal hygiene, and a reverse correlation with the father's education. The only social background factor found to have a strong association was the mother's educational level. This suggests the possibility that the better-educated mother relies less on traditional feeding practices, which are the commonest direct cause of reduced nutrient intake during healthy early infancy and during later illness and convalescence.

Although these findings do not make it possible to reject outright the alternative depicted in Scheme I, they strongly suggest that it is not the social background as such that is interfering with the child's growth and function. If taken together with the large body of evidence that implicates nutritional deprivation in growth failure and with the data on more global behavioral disturbances following malnutrition, they make it seem likely that protein-calorie malnutrition is the intervening variable between social conditions, growth, and intersensory adequacy. Obviously, a definite answer can only be obtained through an anteropective-oriented longitudinal study, in which it would be possible to take environmental circumstances and inadequate nutrition into account without being dependent on a later outcome measurement such as height. Such a

study, which over the next decade will provide a more direct test of the hypothesis, is at present the major endeavor of our research group.

If for all these reasons there is a strong possibility that malnutrition interferes with intersensory organization, a few words about the possible mechanisms of action may be relevant. Theoretically, malnutrition could act either directly, by interfering with the development of the central nervous system, or indirectly. To examine the second possibility first, three mechanisms are readily apparent:

1. *Loss of learning time.* During the periods of malnutrition the child is less responsive to his environment and consequently has less opportunity to learn; at the very least he loses a certain number of months and would therefore be expected to show some long-term developmental lag.

2. *Interference during critical periods of learning.* Experimental evidence has been advanced suggesting that each new function of the brain is sequentially acquired and integrated into the total pattern of performance and experience. Timing is of the utmost importance, since each new function makes its appearance chronologically and is apparently optimal in operation at that particular point. In other words, learning cannot be considered as simply additive. Evidence exists that interference with the learning process at specific times during its development may result in disturbances that are not a simple function of the length of time the organism is deprived of the opportunities for learning; rather, what appears to be important is correlation of the experiential opportunity with a given stage of development. These stages are what is known as "critical periods of learning" (Bowlby, 1962; Scott, 1962 and 1963).

Alterations so produced may be clinically evident immediately, but more often they do not show up until a later age.

The critical periods in human learning have not been definitively established, but some useful information can be derived from an examination of the consequences of interference at

different ages. So far as malnutrition is concerned, the previously cited findings of Cravioto and Robles may be relevant: the mental age of infants under six months of age, as calculated from their psychological test behavior, did not improve, whereas with the older patients the rate of recovery from the initial deficit varied in direct relation to chronological age at admittance. Similarly, the findings of Barrera Moncada (1963) in Venezuelan children and those of Keys *et al.* (1950) in adults point to a marked association between the persistence of later effects on mental performance and the period of onset and the duration of malnutrition.

3. *Motivation and personality changes.* It is a recognized fact that to a considerable extent the infant's reactions determine the mother's response (Thomas, 1963). The diminished responsiveness to stimulation and the emergence of apathy that are one of the first effects of malnutrition may in turn reduce the child's value as a stimulus and thus adult responsiveness to him. Apathy can provoke apathy and contribute to a cumulative pattern of reduced adult-child interaction. This situation has consequences for stimulation, for learning, for maturation, for interpersonal relations, and so on—the end result being a significant risk of backwardness in more complex learning.

The possibility that malnutrition directly affects intersensory organization could stem from its ability to modify the growth and biochemical maturation of the brain. It should be remembered that increase of cell cytoplasm, with extension of axons and dendrites—one of the two main processes morphologically associated with the growth of the human brain at birth—is largely a process of protein synthesis. From microspectrographic investigation of the regenerating nerve fibers, it has been estimated that protein substance multiplies by more than 2,000 as the apolar neuroblast matures into the anterior young horn cell. Perhaps an easier way to grasp the magnitude of this process may be simply to recall that at the time of birth the human brain is gaining weight at a rate of 1 to 2 milligrams per minute. Moreover, as has been

said, changes in the structure of the central nervous systems of animals due to grossly inadequate diets have been documented by Barness (Lowry *et al.*, 1962) and Platt (Platt, Heard, and Stewart, 1964). McCance and associates have shown gross alterations in the content of water and of several electrolytes (Widdowson, Dickerson, and McCance, 1960) in the brain substance, and Flexner and associates (1963) have advanced evidence that interference with protein synthesis in the brain produces loss of memory in mice.

Ambrosius (1960) has reported that in severely malnourished children the normal relation between brain weight and total body weight is distorted. He and his associates have interpreted their findings as an indication of arrested growth of the central nervous system.

It may well be that so-called critical periodicity in behavior represents the responsiveness of the nervous system at a given stage of biochemical organization. If so, nutritional inadequacy may interfere with the staging and timing of the development of both brain and behavior.

Considering that independently of the mechanism involved, the children who showed poor growth also showed delayed development in intersensory functioning, it seems important to discuss the possible significance of the developmental lag to more complex behavioral functioning. Two significant features of learning will be considered: conditioned-reflex formation and the acquisition of academic skills.

In most conditioning situations, what is demanded is the integration of two stimuli each belonging to a different sensory modality. For example, in classical salivary conditioning or in conditioning of leg withdrawal, a taste or a touch stimulus is being linked to an auditory or a visual one. The establishment of equivalences between them is thus required. If interrelations among the sensory modalities are inadequate, conditioning may be either delayed or ineffective. Therefore, if intersensory integration fails to occur at normal age-specific points, a risk of inadequate primary learning at each level can be created.

Alekseeva and Kaplanska-Raiskaya (quoted by Brözek, 1962) have found that protein deficiency often alters conditioned responses in young children. The capacity to elaborate new conditioned reflexes is said to be affected first, but even previously well-established reflex responses may be depressed or abolished. Andriasov and Makarychev (also quoted by Brözek) have reported on animal experiments that confirm the observations made in children. It has been reported that visual-motor control in design copying is dependent on visual-kinesthetic intersensory adequacy (Birch and Lefford, 1964). If it is recognized that, as Baldwin has pointed out, such visual-motor control is essential for learning to write, it becomes apparent that inadequacy in intersensory organization can interfere with this primary educational skill. Moreover, Birch and Belmont, in their studies of reading disability in British and U.S. schoolchildren, have shown that backwardness in reading is far more strongly associated with inadequate auditory-visual integration than with such characteristics as laterality or right-left awareness. A lag in development of certain varieties of intersensory integrations thus appears to have a high correlation with lag in the acquisition of still another primary educational skill.

So the evidence available indicates that inadequacies in intersensory development place the child at risk of failing in his preschool years to establish a normal background of conditionings and of failing in his school years to profit from his exposure to education.

Children with these probable drawbacks are, it is not difficult to realize, more at the mercy of their environment than normal children. Eisenberg (1964) has aptly said that "for the adequately endowed child a variety of environments suffice to permit adequate if not optimal development. For the handicapped child limited in his adaptive capacity there is a considerable restriction in the number of environments within which effective development is possible." Considering the kinds of environment available to malnourished children, what we see in

many older children and adults living in areas with a high prevalence of infantile malnutrition must be a combination of the probable effect of malnutrition *per se* plus the effects of cultural deprivation.

The net result of nutritional deprivation and social impoverishment is what in an ecological sense could be called a circular effect. A low level of adaptive capacity or ignorance or social custom results in malnutrition and produces a large number of people whose functioning is suboptimal and who are themselves more ready to be the victims of ignorance and less effective in social adaptations than would otherwise be the case. In turn, they may rear children under conditions and in a fashion that will produce a new generation of malnourished persons.

Roche: These children tested in the Guatemalan village—were they all from very low-income groups?

Cravioto: No, that is what is interesting. In this community we had some families with incomes of up to four or five thousand pesos per capita a year, which is high for the area; they behave similarly to those with five hundred pesos per capita. Some families do not produce at all, and they were plotted in comparison to this group. In this particular community there is no relation between income and nutritional status, as judged by adequacy in weight, up to the age of six. Beyond six there is a correlation between the two. For the older child and the adult the availability of food or a cash income is a must, but not for the younger child.

Caldeyro-Barcia: What is the difference in nutrition between the tall and the short?

Cravioto: We do not know, because this was not a longitudinal study, but we know some facts—such as that the lack of relationship between the parents' and the child's stature is not primarily genetic but is environmental, although we cannot say whether the cause is infection, nutrition, or something else, or perhaps a combination. What we wanted to test was what the difference in stature brought about by environmental rather than genetic influences

would mean in the way of differences in so-called intellectual performance.

Roche: Dr. Dubos has just asked me to translate a quotation from French. It is this: "Man does not have a nature. What he has is a history."

I have a question: has Dr. Cravioto any explanation of the apparently higher performance at birth of the Latin American and African children as compared to the European?

Cravioto: This high performance has been very well documented. When we started these investigations, we were of course surprised to find it. Fortunately for us, Dean had previously found it in Africa. In all the communities we have studied it has been present; more and more we have seen that it disappears during the first six or seven months of life, and that this is independent of the rate of growth as judged by size or weight. We have no real explanation to offer.

We are now trying to discover whether the premature baby also exhibits this higher rate of development. From this we can go on to whether what we are seeing is not higher but actually lower performance that should not have appeared in the normal full-term infant of a well-developed country—a prior stage, in fact, because these children are born in a state of immaturity. This would not be the first time that higher values proved to be the values of a less rather than a more mature individual.

Zigler: I want to ask about the data on intersensory integration. The figures presented show the undernourished and well-nourished groups as not really being very different except at the earliest stages. It strikes me that it may be erroneous to deduce from data of this kind a real loss of intersensory integration. What I have in mind, Dr. Cravioto, is that performance on your experimental task is the complex result of many variables, and we have discovered in our own research that—especially at very young ages, where you find your large differences—such tasks are highly susceptible to motivational variables; for instance, the reinforcement the child is given for performing the task, his

degree of involvement, his desire to be correct, his possibly having other motives than those of well-nourished children, and so on. What is your evaluation of such a possibility?

Cravioto: The design enables us to eliminate such things as guessing and lack of understanding of instructions; we cannot control, but we can intervene in the sense of reinforcement. What we have are developmental curves; naturally they will meet, and they do, but differently for the different sensory modalities compared. In the haptic-visual, for example, the two come together at nine years, and at that time the level of performance is practically errorless. In the others there are differences, and these differences vary from one comparison to another. What especially interested us was that no such difference could be elicited in the urban group, although the tests were conducted similarly and by the same observers. What we tended to deduce was that there were different levels of performance, and that they were not associated with genetic influences in the urban group and were associated with environmental influences in the same way.

Perhaps Dr. Birch would like to comment, since he is responsible for these types of tests.

Birch: I think that Dr. Zigler raises a very interesting question. Fortunately, we do have some pertinent data, not for this group of children but for others. We have not found that offering rewards or increasing the value of successful performance results in any significant shift in performance levels, at least in this task, among the children we have studied. Most of them come into it very actively involved to begin with. They are most interested, and they keep asking: "Am I right? Am I wrong?" The

kinds of children who may have such problems are those who are mildly subnormal mentally. These children very frequently require additional motivational supports, because they give up as the task proceeds and, unless they are reinforced in certain ways, simply come to perform randomly. This did not appear to be the case in any of the children we are reporting on now.

Waterlow: I should like to ask Dr. Cravioto whether he has any objective evidence about the supposedly bad psychological effects of weaning, particularly premature weaning, which used to be thought such an important cause of subsequent malnutrition.

Cravioto: We have no data yet. Since weaning occurs at a time when a good many other events are also going on, we should like to explore one possibility associated with weaning—the random change in the mother-surrogate. In the villages we are studying at present, the children's age at weaning (in the sense of separation from the mother's breast) ranges from four to eighteen months, but whenever it occurs it is accompanied by this pattern of care. At various times during a single day these children are handled by seven or eight different people for different purposes. We want to learn what the effects are, independent of those of weaning itself. By using a total population, with about two hundred births a year, I think we can get a large enough number of cases that have one variable, and that an important one, but not the other.

Moderator: We now move to psychosocial deprivation and development and call on Dr. Richardson of the Association for the Aid of Crippled Children, New York City.

PSYCHOSOCIAL FACTORS CONTRIBUTING TO DEPRIVATION IN CHILD DEVELOPMENT

Stephen A. Richardson

Deprivation is a general term that cannot be translated directly into a precise, quantitative definition. Rather, it covers a broad territory, which must be mapped out into a series of more carefully defined areas that lend themselves to precise measurement and research. The meaning of the verb *to deprive* encompasses such synonyms as "to dispossess," "to take away," "to hinder from possessing," "to shut out," "to keep from having." There is also the connotation that deprivation occurs because of some inequity—that a child who, for example, died of starvation did so in an environment in which food was available but was not given him because of the fault or neglect of some person or persons or of the economic or political system as a whole. Deprivation occurs when a person does not have something important that he has a right to.*

Also inherent in the term is a value judgment. A person who decides whether any particular case involves deprivation does so always from a position of membership in a particular society and in terms of the values and positions he holds within the society. To some extent he may modify or change his judgment on the basis of the time, place, and set of conditions in which the case of deprivation occurs. For example, he may not regard as deprived a twelve-year-old child who has not learned to read in a nomadic or peasant society where few learn to read, but he will probably judge a child of the same age in a Western urban environment, where almost all children read by this age, to be deprived if he has been

* In scientific research the term *deprivation* is used to describe a procedure in which something is withheld from the experimental group and not from the control group, to determine the effect of the presence or absence of the substance or experience given or withheld.

given no training in reading. Alternatively, another judge adopting a more international frame of reference may decide that the nomadic or peasant society in which the first child lives is deprived as a society in a world where literacy is increasingly important. In this case he would view both children as deprived. Unless the positions of the judge and the person judged are carefully considered, there is real danger of ethnocentrism in deciding whether or not deprivation exists.

Two kinds of evidence can lead us to suspect deprivation. The first is whether the child is able to perform at a given age within the level of expectations and demands that are common to his tribe, society, or national group. Some of these expectations are general to many societies, such as remaining alive, in good health, and without any permanent handicap. Evidence for deprivation then is mortality, morbidity, and the presence of a permanent handicap. Other expectations for the child vary depending on the skills and talents needed by the society in which he lives. Some societies may stress for boys physical stamina, agility, and strength for hunting; others may emphasize intellectual and conceptual abilities for the skills needed in a technologically advanced, industrialized, urban way of life.

The second kind of evidence needed to judge a case of deprivation involves the child's upbringing and experiences. Every society throughout time has evolved child-rearing practices that give the child a complex array of experiences designed to preserve life, maintain health, avoid chronic or handicapping conditions, and develop physical motor, intellectual, sensory, and social skills that prepare the child for life as an adult in his society. If a child does not receive the elements of upbringing or experience essential

for development, this is evidence of deprivation.

These two kinds of evidence—of whether a child fails to live up to expectations and of whether he has not had the experiences necessary to prepare him to meet these expectations—are both needed to make a judgment. The task would be simpler if in addition there was evidence that the absence or paucity of some care or experience was the cause of the child's inability to perform later at the level expected of him. We do not know, for example, whether an acute episode of malnutrition at the age of two years causes mental retardation and thus incapacitates the child to meet the levels of intellectual performance expected of him when he is ten. We do know that this simple cause-and-effect example is a gross oversimplification. In nearly all cases, a child's inability to meet his parents' or others' expectations by an outcome measure, physical, intellectual or social, is the result of a complex cumulative sequence of events, circumstances, and conditions spread over a period of time. We rarely know all the kinds of experiences the child may have missed—the adequacy of his fetal development, the kinds of prenatal insults to which he may have been exposed, and, in his postnatal life, the quality of his maternal care and intellectual and social stimulation. Studies, using large numbers of cases, of the association between mental subnormality (inability to meet expectations of adults) and antecedent factors have showed that mental subnormality occurs more often in lower-class than in upper-class families (Masland *et al.*, 1958). These differences in life styles encompassed in the concept of social class evolved over a time span far longer than the child's life. We have evidence that mental subnormality is associated with pregnancy complications (Masland *et al.*, 1958; McMann and Sowa, 1961). But we also know from the work of Baird and his associates that pregnancy and delivery complications occur more frequently in lower- than in upper-class women. There appears, then, to be some complex interaction among membership in the lower class, complications of pregnancy and delivery, and

mental subnormality (Illsey and Fairweather, 1960). Kwashiorkor in infancy would be taken as strong evidence of deprivation. But the range of evidence needed to identify the essential experiences that lead to kwashiorkor is extremely complex, as is shown by the case of a certain Central American child admitted to a hospital at the age of two with kwashiorkor. The mother reported that her husband had become an alcoholic and deserted her eighteen months previously. To support her five children, she took a job in a tortilla factory, working about six hours a day and earning fifteen cents plus a dozen tortillas. While she worked at the factory, the children were left without any adult care. The youngest child came down with chronic diarrhea, and she put him on an *atole* diet. Kwashiorkor developed, and she then brought the child to the hospital.

The experiences of this child are related to the general historical and political conditions of the country, the social and economic conditions of the urban slums surrounding the city, the level of hygiene, the social pathology of the family, the mother's being forced to work, her values, her training in how to care for chronic diarrhea, and the kinds of advice that she felt were available to her and that she would use.

The value to scientific research of the concept of deprivation is to direct inquiry into areas in which we need more knowledge about what experiences are necessary to enable children to meet the expectations of the society they live in. Socially and psychologically, for example, we must explore whether certain patterns of child care differentiate children with different rates of physical growth; whether certain forms of residential institutional care do not provide children with love and support, play, opportunities to explore a colorful and varied physical environment, and sufficient time with adults for adequate development of speech; whether these experiences are necessary for adequate socialization. Much work of this kind has been attempted and will be the subject of this paper. Most of it, however, has been done in Westernized industrial societies, and we

should remain alert to the danger of both the ethnocentric view of the investigator and the cultural conditions in which the work took place. There can be ethnocentrism in adherence to a particular scientific approach, theory, or viewpoint as well as in the selection of a topic for investigation.

Social Factors Associated With Mortality, Morbidity, and Handicap

An important body of research findings relating childhood mortality, morbidity, and handicapping conditions to social environmental factors has been obtained by means of epidemiology. Although epidemiology developed in the search for the causes of diseases such as pellagra, cholera, typhoid, and malaria, it has increasingly been used for the study of disabling conditions such as mental subnormality, reading handicaps, school dropout, psychiatric disorders, and juvenile delinquency—conditions that prevent the child or young person from performing in a way expected of him by society. Whereas some of the classical studies of epidemiology were able to track down the insult that caused the disease state, more recent studies deal with impaired functioning in which the causes are probably multiple and cumulative, and in which little is to be learned about a particular instance by identifying the conditions under which the impairment is most likely to occur.

The most common social variable used in epidemiology is "social class." This is usually measured by the occupation of the child's father, with the occupations then classified into a number of categories in which distinctive styles of life are believed to occur. More complex measures of social class sometimes include income and the education of the parents. Numerous studies have found that the rates of mortality, morbidity, and various forms of functional impairment in children are higher in the lower social classes. Relationships have also been found between lower social class and greater frequency of infant mortality, prematurity, epidemic and infectious diseases, bron-

chitis, pneumonia and tuberculosis, rheumatic heart disease, ulcer, and cancer of the stomach (Susser and Watson, 1962, p. 82).

Other social variables used are race and ethnicity. Negroes in the United States and the colored South African population compare poorly with whites on most measures of health (Susser and Watson, 1962). Minority groups such as Spanish Americans in the United States, French Canadians, and Indians in Central America are frequently found to have higher rates of infant mortality and childhood morbidity. Ethnic and racial minority groups are found most often in the lowest social class, where poverty is greatest. And along with this poverty are other factors that have been shown to be associated with higher mortality and morbidity—high parity, close spacing of children, pre-nuptial conception and illegitimacy, poor hygiene, broken homes, and mothers leaving young children to take unskilled employment for bare subsistence.

Shifts in the Viewpoint and Interests of Scientists

The close association between poverty and a wide variety of indicators of physical and social pathology has been known for a long time, but until recently few scientists have gone further than demonstrating its existence. Perhaps the apathy in the face of such powerful findings may be accounted for in part by the widespread belief in theories of constitutional inferiority, the process of natural selection, and such economic views as the iron law of oligarchy. These theories led to a viewpoint and values rather similar to those of McFarland, who is quoted in the 1960 edition of the *Encyclopaedia Britannica* as having written, in 1782, "In tracing the causes of poverty, I have endeavored to show that the greatest number of those who are now objects of charity are either such as have reduced themselves to this situation by sloth and vice, or such as, by a very moderate degree of industry and frugality, might have prevented indigence."

There is, however, increasing interest and attention to the view that poverty, with all the

associated deprivation, is not a necessary state of any society. Many forces are encouraging this view: the growing number of independent nations that previously were under colonial rule; the civil-rights movement, which is challenging the traditional caste treatment of the Negro; the growing demand for training and education as technological development reduces the need for unskilled labor; and an increasing recognition of the need for dealing with a wide variety of deprivation and social pathology through prevention, rather than through treatment in such forms as social welfare, crime detection and punishment, or the provision of health services. In the United States, this interest is manifested by the antipoverty program, the new educational legislation for providing enrichment programs to deprived children, and recent and pending civil-rights legislation.

This general developing interest in factors that contribute to deprivation in children has influenced research. Although scientific interest still continues in genetics and biochemistry and in innate mechanisms that influence growth, greater emphasis is now being given to environmental factors, both biological and social. In recent reviews of mental subnormality (Masland *et al.*, 1958; Penrose, 1954; Knobloch and Pasamanick, 1962), the authors estimate that genetic and chromosomal abnormalities contribute only a minor proportion of all cases of mental subnormality as compared with biological and social environmental factors before and after birth. This shift in emphasis is strongly expressed by Pasamanick (1959, p. 318):

Except for a few hereditary clinical deficiencies and for exogenous injury to neural integration, behavior variation does not seem to be the result of genetically determined structural origin. It is now possible to entertain a new *tabula rasa* theory hypothesizing that at conception individuals are quite alike in intellectual endowment except for these quite rare hereditary neurologic defects. It appears to us that it is life experience and the sociocultural milieu influencing biological and psychological function which, in the absence of organic brain damage, makes human beings significantly different behaviorally from each other.

To explore this challenging hypothesis, it becomes necessary to go beyond the essential first step of studying the associations between mortality, morbidity, and handicap and demographic variables such as social class, race, and ethnicity and to seek to identify specific factors in the general style of life broadly identified by these general variables that contribute to differential rates of pathology or different levels of functioning. Essential to the development of this approach is careful and systematic description of the child in the context of his family environment.

A pioneer study of this kind was a pediatric investigation conducted by Sir James Spence and his colleagues in Newcastle-upon-Tyne. Their purpose was "to identify the diseases of childhood in a representative sample of families, to trace their origins, and to measure their effects" (Spence *et al.*, 1954). About a thousand families were studied over a span of several years. In introducing the second report of the study (Miller *et al.*, 1960), they state:

We shall show that the occurrence and natural history of illness can be understood only if it is regarded as an aspect of the community in which it occurs, and that when illness develops in a growing child the pattern and outcome are influenced by the child's environment as well as by the particular agents of infection or injury. Indeed we think we could go further and suggest that some disorders such as pneumonia are almost an expression of family environment. (Introduction, page B)

In examining frequency of illness and condition of risk, these investigators found that children in lower-class families had bronchitis, pneumonia, staphylococcal diseases, convulsions, and infectious diseases more frequently than children of higher social status. Going beyond the gross classification of social class, the investigators described, defined, and classified for purposes of analysis features of the family environment that they believed contributed to the children's level of health: the mother's care, the structural environment of the housing, the human environment of the family, and a series

of factors by which an index could be constructed of problem families. When these measures of social and physical environment were related to the children's diseases, associations were obtained where none had been evident on the basis of the unrefined classifications of social class. For example, although no significant relationship was found between alimentary infections and social class, significant relationships were found between these diseases and deficiency of supervision, clothing, personal cleanliness, and sleep and sleeping arrangements. The investigators were impressed by the importance of the quality of the mothers' care as the chief single factor in the welfare of the infants. In their conclusions, they also emphasize the complex interrelationships and cumulativeness of biological and social environmental factors in the causation of disease.

Social and Psychological Factors That Influence Social-Psychological Development

There have been a number of careful sociological descriptions of child development in socially and culturally deprived groups. Davis and Dollard (1940), through case histories of Negro children in Louisiana, make vivid the ways in which the white person is taught the social dogma of his caste with regard to Negroes, the rigidity of the caste system, its effect on the personality development and aspirations of Negro children, and particularly the human bitterness and resentment engendered by their childhood experiences.

Oscar Lewis, in *Five Families and Children of Sanchez*, presents detailed case histories of Mexican families in rural and urban environments and shows some of the social environmental factors that influence the children's growth and development. Although he does not deal specifically with children, Caudill (1962) shows the social effects of industrial exploitation in Kentucky and the poverty of the region when the mines closed down. The following composite description given by Martin Deutsch (1964, pp. 252-3) of lower-class

life illustrates the kinds of leads for further work that such descriptions provide.*

Geographically, there are crowded and dilapidated tenements quite at variance with the TV image of how people live. If the people are Negro, Puerto Rican or Mexican-American, or poor mountain white, life is in a more-or-less segregated community. There are likely to be extremely crowded apartments, high rates of unemployment, chronic economic insecurity, a disproportionate number of broken families, and (particularly in the case of the Negro) continual exposure to denigration and social ostracism of varying degrees. The educational level of the adults tends to be quite limited. In the homes, there is likely to be a nearly complete absence of books, relatively few toys, and, in many instances, nothing except a few normal home-objects which may be adapted as playthings. In addition—particularly but not exclusively where relatively new in-migrants are concerned—there is a great deal of horizontal mobility. The result is a pattern of life that exposes a child to a minimum of direct contacts with the central channels of our culture. The conditions of social inequality, the absence of an accessible opportunity structure, and the frequent non-availability of successful adult male models create an atmosphere that is just not facilitating to individual development. Moreover, the everyday problems of living, particularly those of economic insecurity and a multiplicity of children, leave minimum time for the adults who may be present to assist the child in exploring the world, to reward him for successful completion of tasks, or to help him in the development of a differentiated self-concept. Even in homes which are not broken, the practical manifestations of economic marginality result in the father sometimes holding two jobs and having little time for interaction with the child. We have found in various studies that children from these circumstances have relatively few shared or planned family activities, again resulting in a narrowing of experience.

The value of these and other descriptions is that they provide an opportunity for identifying variables in the social environment for further, more systematic, specifically focused quantitative study and offer insights that may become the basis for further studies.

There is good evidence that children of the

* For "a portrait of the underprivileged," see also Frank Riessman, *The Culturally Deprived Child*, Harper and Row, New York, Evanston and London, 1962, pp. 26-35.

lowest social class, especially if they come from stigmatized minority or ethnic groups, perform less well generally on a wide range of measures—school grades, dropping out of school at earlier ages, and failure to finish high school. The frequency with which lower-class children are provided an education inferior to that of other children has also been made clear in terms of such measures as the professional-to-pupil ratio, per-pupil expenditure, quality and experience of teachers, and proportion of school time spent in teaching (Conant, 1961; Sexton, 1961; Douglas, 1964). Studies by Martin Deutsch and his colleagues (1964, p. 254) have shown that differences in school performance between children of lower and higher social classes emerge at early ages:

The overwhelming finding of studies on the relationship between social class and learning, school performance, and the like is that children from backgrounds of social marginality enter the first grade already behind their middle-class counterparts in a number of skills related to scholastic achievement. They are simply less prepared to meet the demands of the school and the classroom situation. Conversely, though, the school has failed to prepare to meet their needs. The failure of the educational institution to overcome the children's environmentally determined handicaps too often results in early failure, increasing alienation, and an increasingly greater gap between the lower-class and middle-class youngsters as they progress through school. In other words, intellectual and achievement differences between lower-class and middle-class children are smallest at the first grade level, and tend to increase through the elementary school years.

The findings of poorer performance at school entry for lower-class marginal children had no beneficial consequences for these children so long as the explanation was thought to be genetic or intelligence was regarded as innate and fixed. With increasing evidence of the postulated importance of the social environment in influencing cognitive development, however, differences in performance at school entry have led to two rapidly developing bodies of research and action. In research, studies are now investigating the nature of the early environment to determine whether socially mar-

ginal children are being deprived of experiences necessary for later adequate growth and development. In action, a widespread program is getting under way in the United States to better prepare children to meet the expectations and demands they will encounter in school. A great deal of thought and attention is going into the nature of these pre-school "enrichment" programs. In this paper, however, I shall focus on some of the social science research on socially marginal children. Because many of these studies are still under way, perhaps the most useful form of reporting is to illustrate the kinds of questions and hypotheses that guide the work and some of the variables being studied.

A major emphasis in these recent studies has been in sensory development—in identifying the kinds of environment and experiences necessary for the adequate development of auditory reception and discrimination of language, and of visual and tactile learning. This probably stems from the interest of educators in the development of cognitive skills, from some evidence that sensory development is more sensitive to environmental influences than motor development (see Hunt, 1964), and from reports of differences in perception between and within cultures (Allport and Pettigrew, 1957; Bagby, 1957; Nissen, Machover, and Kinder, 1935; Rivers, 1901, 1905; Segall, Campbell, and Herskovits, 1963; Sherif, 1935; Tresselt, 1948; Woodworth, 1910).

J. McV. Hunt (1964) has speculated that infants exposed to the crowded conditions of lower-class slums may not be handicapped by the diversity and level of visual and auditory inputs during the first year of life but that during the second year

as the infant begins to throw things and as he begins to develop his own methods of locomotion, he is likely to find himself getting in the way of adults already made ill-tempered by their own discomforts and by the fact that they are getting in each other's way. In such a crowded atmosphere, the activities in which the child must indulge for the development of his own interests and skills must almost inevitably be sharply curbed.

Beginning in the third year, moreover, imitation of novel patterns should presumably be well established, and should supply a mechanism for learning vocal language. The variety of linguistic patterns available for imitation in the models provided by lower-class adults is both highly limited and wrong for the standards of later schooling. Furthermore, when the infant has developed a number of pseudo-words and has achieved the "learning set" that "things have names" and begins asking "what's that?", he is all too unlikely to get answers. Or, the answers he gets are all too likely to be so punishing that they inhibit such questioning. The fact that his parents are preoccupied with the problems associated with their poverty and their crowded living conditions leaves them with little capacity to be concerned with what they conceive to be the senseless questions of a prattling infant. With things to play with and room to play in highly limited, the circumstances of the crowded lower class offer little opportunity for the kinds of environmental encounters required to keep a two-year-old youngster developing at all, and certainly not at an optimal rate and not in the direction demanded for adaptation in a highly technological culture. (p. 238)

There is some indirect evidence in support of these speculations. Fifth-grade lower-class Negro and white children were given the Wepman Auditory Discrimination test (see Cynthia P. Deutsch, 1964). In this test, pairs of words that sound very much alike are presented to the child and he is asked to say whether the pairs are the same or different. These children scored well below the norms established for the test.

Hess (1965) is conducting a laboratory experiment in which mothers and their young children participate in a task that requires close cooperation for successful completion. The discussion between each mother and child is systematically analyzed. Compared with middle-class mothers, lower-class mothers provide less information to the child and less opportunity for him to share in planning the task.

It is widely believed that the parents or caretaker of a young child are of crucial importance in the child's acquisition of language. Factors that influence the learning process include the amount and nature of the adult speech the child listens to, the extent to which his attempts at speech are encouraged and

corrected, whether the development of questioning is helped or hindered, and the quality and quantity of adult speech. If the young child spends most of his time with older brothers and sisters or other children and little with adults, the speech he learns from will be more rudimentary than adult speech. Martin Deutsch (in Passow, 1963), studying the nature of conversation between adults in middle- and lower-class families, has found that sustained conversation in lower-class homes is far shorter. Studies by Bernstein (1965) of middle- and lower-class language usage by British children show that lower-class children use far less complex patterns of speech; short, grammatically simple, often unfinished sentences; and less conceptual language. Although their vocabulary may be quite rich expressively, it is not the vocabulary likely to be encountered among teachers in school (Eels *et al.*, 1951). John and Goldstein (1964), in examining social conditions that affect language acquisition, are studying "the gradual shift in the child's use of words, from labeling specific and often single referents to the use of words for signifying categories of objects, actions, or attributes." They hypothesize "that the rate and breadth of this shift varies from one social context to another, and that it has differential consequences for cognitive development dependent on the social context in which it occurs." Nisbett (1953) has carefully reviewed "the slight but definitely established tendency for intelligent children to be found in small families and dull children in large families." This tendency persists even when such factors as parents' occupation or overcrowding in the home have been controlled for. He believes the results may in part be explained by "the environmental influence of the size of the family on verbal ability and through it on general mental development."

Although the influences of an impoverished social environment on oral discrimination and speech development is a major issue now under investigation, there is also interest in what influences the development of visual and motor

sensory skills. In impoverished homes there is likely to be an absence or a paucity of toys, especially the kinds of objects that will be encountered later in school—pencil and paper, crayons, blocks, modeling clay. The home and immediate environment in slum areas are less likely to have a wide variety of pictures and books, and the child is less likely to be taken to a variety of environments beyond his home and its immediate surroundings. In a survey, as yet unpublished, of reading ability for the total population of seven- to twelve-year-old children in Aberdeen, Scotland, we have found that the reading-test performance of children whose fathers are manual workers is poorer than that of children whose fathers have non-manual occupations.

Clearly, consideration of the various sensory modalities is only the first step toward consideration of the interrelationships among sensory skills and their development and of various hierarchical organizations of the different sensory modalities. Birch and Lefford (1963) have been developing methods for approaching the study of intersensory perception and developing norms for their test. For example, in one test, the children are asked to listen to a series of dots tapped out with a pencil and then to identify this pattern from three alternatives shown visually. Birch, Belmont, and Karp (1964, 1965) find a positive correlation between audiovisual integration as measured by this test and reading ability in first- and second-grade children. They have found also that children who were retarded in learning to read performed more poorly on the test than normal readers.

Children who live in lower-class, minority, or stigmatized groups generally have little personal contact with members of the middle class or the majority group before they reach school age. Yet in many ways they learn many of the upper- and middle-class values and begin to recognize that they and their families do not conform to these values and expectations. The effect on their personality development has been well summarized by Clark (1955):

As minority-group children learn the inferior status to which they are assigned and observe that they are usually segregated and isolated from the more privileged members of their society, they react with deep feelings of inferiority and with a sense of personal humiliation. Many of them become confused about their own personal worth. Like all other human beings, they require a sense of personal dignity and social support for positive self-esteem. Almost nowhere in the larger society, however, do we find their own dignity as human beings respected or protected. Under these conditions, minority-group children develop conflicts with regard to their feelings about themselves and about the values of the group with which they are identified. . . . These conflicts, confusions, and doubts give rise under certain circumstances to self-hatred and rejection of their own group.

Minority-group children of all social and economic classes often react to their group conflicts by the adoption of a generally defeatist attitude and a lowering of personal ambition.

A number of specific skills are expected of schoolchildren by their teachers, who are predominantly middle-class in their orientation and values. They expect the children to have a good time sense, to know how to approach a task in an orderly manner, to be able to pay attention to them. But many of the children from low-social-class backgrounds have received little training in these skills and values, and usually their parents have not been good examples or role models. They have had little experience in listening to sustained adult talk, particularly middle-class speech patterns. Because they live in crowded and noisy homes, they may, in fact, have learned to be inattentive to talk. Studies of schools have shown that readers and other textbooks generally portray scenes of upper- and middle-class suburban and rural life, and there is considerable evidence that the various standard aptitude tests discriminate against lower-class children by the selection of items that include words, scenes, and events with which lower-class children have little or no familiarity. Teachers live in a social milieu and under conditions very different from those of the deprived child and have generally learned the middle-class set of values. They have had little experience

of the day-to-day conditions in which he lives and little understanding of his behavior. Furthermore, not only may the deprived child be unable to meet their expectations and demands but his failure may well be interpreted as evidence of poor heredity and a low and fixed level of intelligence. On the basis of this interpretation, teachers may feel that there is little they can do and hence may adopt a defeatist attitude.

Possibly one of the factors most damaging to self-esteem is failure to live up to the expectations and demands of others. The widespread evidence of poorer performance by lower-class children suggests a frequency of such failure that may kill any early interest a child may have had in school and cause him to seek his successes and satisfaction with his peers, with whom in general he has far more contact, and to seek less contact with adults than the middle-class child enjoys.

The segregation of the deprived child along class, racial, and ethnic lines frequently occurs not only in his home environment but also in his school. Almost all his social and learning experiences except for contact with his teachers, exposure to the mass media, and occasional brief encounters with middle-class people reinforce the norms and values of his subculture and build up behavior patterns that make it increasingly difficult for him to perform as an adult in ways expected by the majority culture. Studies of the ways in which lower- and middle-class children describe themselves show the lower-class child to be more fatalistic and feel he can do less to control or have autonomy over his environment than the middle-class child; to have lower self-esteem; and to be more conflicted and confused about his identity (Brim, *et al.*, 1965; Battle and Rotter, 31).

There is good evidence that if the child has a stigmatized skin color he early learns its implications for social status and personal worth (Clark and Clark, 1939; Goodman, 1952). The effects of segregation are as harmful for whites as for Negroes. Clark (1960) writes:

Segregated education is inferior and nonadaptive for white as well as Negroes. Put simply, no child can receive a democratic education in a nondemocratic school. A white youngster in a homogeneous, isolated "hot house" type of school situation is not being prepared for the realities of the contemporary and future world. Such a child may have brilliant college entrance scores, be extraordinary in his mathematical ability, or read and speak a foreign language with skill and precision, but he is likely to be blocked in many circumstances in his ability to use these intellectual abilities with the poise and effectiveness essential to personal and social creativity. A racially segregated school imposes upon white children the inevitable stultifying burdens of petty provincialism, irrational fears and hatreds of people who are different and a distorted image of themselves. Psychologically, the racially segregated school at this period of American and world history is an anachronism which our nation cannot afford. This point must be made over and over again until it is understood by those who have the power to make the decisions which control our destiny.

Effects of Change of Environment on Performance

A crucial test of the extent to which lack of certain experiences leads to inability to measure up to an expected level of development is whether changes in the environment lead to changed levels of performance. A number of studies suggest the effectiveness, for performance change, of providing experiences postulated as necessary for certain training. When mentally subnormal children between the ages of three and six were given a special nursery-school experience, their intellectual growth rates were found to be accelerated in comparison with those of a control group that did not have this experience (Kirk, 1958). Tizard (1964) created a special residential unit for severely retarded children aged eight who had previously lived in a large institution. He selected sixteen pairs of children matched for sex, age, IQ, and, as far as possible, diagnosis. The experimental group were then moved to a small residential unit and given a program of care and education specially designed to provide them with experiences the author believed necessary for optimum growth

and development; the controls were left behind in the institution. After two years, the experimental group were found to be advanced in many ways over the control children. An early extensive study of the consequences of nursery-school attendance (B. L. Wellman, 1940) showed that it has an effect measurable not only at the end of nursery school but for several years thereafter. Klineberg (1935 and 1963) studied school records and intelligence tests of Negro children in the North and the South and provided a wide variety of evidence to show the positive effects on IQ's of improved educational environments.

Another form of natural experiment that has been used to determine the effects of environment on development has been to study children reared in institutions who have received adequate physical maintenance but very few of the other experiences postulated as necessary for adequate over-all development. The studies show that these children have a higher mortality rate; are slower in learning motor functions such as sitting, standing, and walking; are retarded in cognitive functioning; and have disturbed emotional reactions and apathetic responses to social environment (Ainsworth *et al.*, 1962; Bowlby, 1962; Dennis, 1960; Dennis and Dennis, 1941).

These illustrations provide encouragement for further research into the mechanisms whereby social environmental conditions can influence the growth and development of children socially and biologically.

At the outset of this paper, I warned of the need to remain alert to the danger of being culture-bound and ethnocentric in judging what constitutes deprivation. At this point, having reviewed some of the research, let us see to what extent it would be judged pertinent in terms of the United Nations Declaration of the Rights of the Child, using the reasoning that a child who does not receive what is rightfully his is thereby deprived. Because this document was unanimously adopted by the United Nations General Assembly—on November 20, 1959—it is unlikely to express

a narrow or ethnocentric viewpoint. Although the Declaration sets a standard that its authors believe all people seek to achieve, rather than reflecting existing conditions, it does provide a valuable set of criteria both for conditions believed essential to adequate development and for desirable goals for young people. Its principles contain five approaches to the consideration of the child's rights:

1. The set of international, political, and social conditions that are necessary for the healthy functioning of the society or country in which the child lives.

Principle 10: "He shall be brought up in a spirit of understanding, tolerance, friendship among peoples, peace and universal brotherhood."

2. The social conditions the child is born into and in which he is reared.

Principle 1: "All children without any exception whatsoever, shall be entitled to these rights, without distinction or discrimination on account of race, color, sex, language, religion, political or other opinion, national or social origin, property, birth or other status, whether of himself or of his family."

This implies that many children at present are deprived as a result of these considerations.

3. The experiences the child must have for optimal growth and development of his potentialities.

Principle 4: ". . . adequate pre-natal and post-natal care . . . , adequate nutrition, housing, recreation and medical services."

Principle 6: ". . . love and understanding, . . . moral and material security, in the care and under the responsibility of his parents."

Principle 7: ". . . play and recreation . . . , and education which will promote his general culture. . . ."

4. The level of functioning at different stages in the child's development necessary to meet the expectations of the society in which he lives.

Principle 2: "To develop physically, mentally, morally, spiritually, and socially in a healthy and normal manner."

Principle 6: ". . . the full and harmonious development of his personality. . . ."

Principle 7: ". . . to develop his abilities, his individual judgment and his sense of moral and social

responsibility and to become a useful member of society."

Principle 10: ". . . that his energy and talents should be devoted to the service of his fellow men."

5. Special provisions and care for children who, in the widest sense of the term, are handicapped.

Principle 5: "The child who is physically, mentally or socially handicapped shall be given the special treatment, education and care required by his particular condition."

The implication is that without such care the child might suffer deprivation.

Of these five ways of viewing childhood deprivation, I have stunted the first and last. The contribution of wars, revolutions, and social inequities resulting from governmental and political action has been demonstrated in countless tragedies to lead to widespread deprivation. There is a developing interest in subjecting these problems to systematic scientific inquiry. The special provisions and care needed for handicapped children from the point of view of social and psychological consequences of handicapping I have, in part, reviewed elsewhere (Richardson, August 1963; see also Birch, 1964). The remaining three approaches expressed in the Declaration of the Rights of the Child are close to those used in this paper.

The research reviewed in the present paper was conducted almost entirely within the context of Western industrial society. Its emphasis on learning and on the abilities prized by educated people reflect the values of the more educated segment of the society. This is an ethnocentric view, and there are certainly abilities that deprived children develop to a greater extent than other children. These I have neglected to examine. I have also neglected to examine what forms of deprivation privileged children in the society may be subjected to. Between and within countries the kinds of demands and expectations placed on children will vary, but in all countries there are demands and expectations and there will be some children who will have difficulty meeting them because they lack experiences essential for

their growth and development. The task of the investigator is to identify the values and aspirations of the culture or society in which he is to work and, if they are compatible with his ethics, to adapt to them some of the research approaches and methods developed in other countries.

The need to consider largely separately the social and psychological factors and the biological factors contributing to deprivation reflects the traditional separation of the biological and social sciences. Increasingly there is a need for designing studies that consider both biological and social factors and their complex interplay in child development.

Although there will always be an important role for laboratory experimentation, increasingly there is a need for studies that use defined samples or populations of children and study the circumstances and conditions of child growth before the diagnosis is made of ill health or functional impairment. As yet we have relatively little experience in designing and executing such ecological studies. Prerequisite for them is the existence of teams of investigators whose members represent both the biological and social sciences, who can stay together over a period of years, and who develop a mutual respect and intelligent understanding.

The goal of research into deprivation is prevention. In the past, there has been no shortage of social action to prevent deprivation. What has been missing and is now slowly and painfully beginning to emerge is the concepts and methods necessary for systematic analysis of the mechanisms that cause deprivation. As these are used and defined and our knowledge grows, it may be possible in political and social action to come closer to the medical dictum *Primum non nocere* and to provide the better conditions necessary for the optimum development of children.

Moderator: Because of his special interest in and contributions to this subject, Dr. Edward F. Zigler of Yale University has been invited to open the discussion of this paper.

Discussion: Edward F. Zigler

I must repeat a remark I made to Dr. Richardson earlier: that I am awed by his bravery in even attacking a subject of this magnitude and complexity. I have now been wallowing, if not drowning, in the literature on social and cultural deprivation for the past ten years. If I were to make one minor complaint about Dr. Richardson's presentation, it is that it does not quite give the flavor of the controversy—of the sloppiness, if you will, and the tremendous differences of opinion that are to be found in this literature.

To give a notion of its magnitude, a student working with me labored one solid year putting together a review of this literature. The bibliography alone is thirty-five pages and its entries number in the hundreds. By picking and choosing through this literature, one can find any point of view about deprivation and its effects that one likes.

The problem of definition itself is almost an impossible one. Perhaps the best definition I have heard was advanced some years ago by Jack Gewirtz, who said: "Social deprivation refers to some state of affairs in childhood which has subsequent effect later in life, except no one can agree on the early state of affairs or the subsequent effects."

Now, the "early state of affairs" aspect of the problem has been almost fadlike in its changes from decade to decade. A number of years ago the essential component of deprivation was thought to be something to do with mothers, and there was much concern on the part of Spitz, Ribble, Bowlby, and others who seemed to think that lack of mothering was the essential ingredient of deprivation.

With the reviews of Orlansky and Pinneau, mothers became a little less prominent in our thinking. This concern was followed by some others. Recently deprivation has been aligned mostly with notions of sensory deprivation, primarily as a result of the studies of Hebb and other workers in Montreal. In fact, it is not uncommon to find theoretical discussions

of deprivation in which the deprived child is considered somewhat analogous to Hebb's sensorially deprived animals. This makes little sense, since the milieu of the deprived child is one in which he receives tremendous amounts of sensory input. So now theoreticians are stuck again and are thinking in terms of some optimal level of stimulation as being the essential aspect.

At any rate, it is very clear that we are going to make very little headway, as Dr. Richardson has pointed out, if we equate social class with deprivation. What is badly needed is some careful delineation of the concept itself. It must be reduced to a collection of socio-psychological processes. If it is a matter of sensory input, let us study sensory input. If it is a matter of child-rearing, let us study child-rearing. But the analysis of the concept must be carried out at the level of our dependent variables.

Concern with cultural deprivation in this country has coincided over the past ten years with a tremendous concern with intellectual and cognitive growth and development. As a result, most of the people who are interested in deprivation seem to see as its primary effect some poor or abnormal development in intellectual functioning. There has been a tremendous emphasis here on cognitive development, with the accompanying view that its attenuation is a result of cultural deprivation.

This raises certain theoretical issues that have been overlooked, in my opinion, by typical American investigators. I think that they have predecided an issue that is still open for controversy and investigation: the basic issue of the exact relationship between experience and the growth of the intellect. It is very appropriate that there have been two quotations here today, one from Locke and one from Socrates, because the positions of these two philosophers still identify the ends of a continuum. Unfortunately, there has been no synthesis of these two positions in our con-

ceptualization of intellectual development. The Socratic-Platonic position is certainly in keeping with those who have emphasized the hereditary nature of intelligence, the nativistic and autochthonous component of cognitive development.

We can find this position in the pre-deterministic notions that were very prominent during the heyday of Gesell. Stated in its extreme form, the view was that the organism is uninfluenced by experience. We all remember the little homunculus we used to see in that one drop of semen. The notion was that everything that characterized the organism was there at the moment of conception and that development was some unfolding or flowering of the organism, independent of experience.

The other end of the continuum is Lockean. It is an experiential position that argues that the organism is almost completely plastic and that the final product we see in intelligence is simply a result of the experiences of the organism. This position is found in most American learning theories; it is clearly seen in the radical empiricism of a Skinner, and earlier in the position of Watson. This *tabula rasa* position, with its experiential emphasis, is now dominant in U.S. thinking on the culturally deprived child. Its most outstanding contemporary spokesman is J. McVickers Hunt, and it is certainly to be found in his book *Intelligence and Experience*. I think it can also be found in the cognitive work of Bruner, where the emphasis is on "technology." The suggestion here is that if we can just find the right way to teach the child, we can make him into anything we like.

Of course, either of these positions taken to an extreme is considered more or less bankrupt. There is a third position to which everyone at least gives lip service. This, of course, is the interactionist position: that what matters is not heredity alone, not experience alone, but some complex interaction between these two factors. Unfortunately, this correct insight has not led to a careful point-by-point exploration of the nature of the interaction. Its most out-

standing spokesmen are Piaget and his followers. Their discussions of accommodation, assimilation, and equilibration, though interesting, do not really explicate the role of experience in cognitive development.

The many and diverse possibilities have not been adequately considered by the theoreticians. For instance, the position might be taken that every experience encountered by the organism is important and influences cognitive development. I think one must take such a position if one deals in terms of the habit strengths of a Hull or the functional relationships between rewards and responses emphasized by someone like Skinner.

There is also the possibility, mentioned here today, that each experience is not important in itself but that there must be points in cognitive development at which instead of assimilating—to use the language of Piaget—the organism must now accommodate, must now go to a new equilibration. This suggests some notion that experience is crucial at critical periods falling at various points in the life cycle.

A third possibility, one that is close to the Platonist's heart, is that experience is nothing more nor less than the fertilizer, the manure, of human cognitive development. The view here is that within a very broad range of experience it does not make much difference what one encounters. So long as one encounters experiences within this range, one will develop the structures that are truly cognitive in nature.

Whatever the answer may be, we must not lose sight of individual variation in intellectual capacity. I am becoming concerned by the tendency of American workers in the area of social deprivation to be so Lockean in their approach. It has become terribly unfashionable to even talk about individual variation in intellectual capacity. I am very much afraid that we have let our values interfere with our scientific good sense.

In a very fine article in *Science* a year or two ago, Hirsch made the correct assertion that individual variation is a law of biology and

that we do no one a service by ignoring it. Indeed, we may do a disservice to the very children we are trying to help. What I have in mind is that the experiential people always are looking for some panacea for the child's cultural deprivation. Do "this" and the child will not manifest any cognitive shortcomings. If not "this," then do "that." Implicit is the view that there is some single experiential event or set of events that is equally effective across all genetic compositions. If there is one thing that behavioral geneticists have demonstrated, it is that the same experience quite differently affects organisms having different genetic compositions.

This problem of cognitive development and experience has been especially crucial in respect to mental retardation. Dr. Richardson quotes in his paper a position I find untenable—that in almost every instance where there is no obvious pathology, mental retardation is a case of some kind of cultural deprivation.

Richardson: The Pasamanick position infers biological insult, as well as social environmental factors.

Zigler: Yes, but a position that I should like to put forward as a possibility—one that seems unpopular today—is that there is basic human variation in intelligence, just as there is human variation in any complex trait we have investigated, and that even given optimal experiences there will always be such variation. To consider that the child who is not terribly bright or is even stupid, for that matter, is always the product of some kind of physiological defect, as the Russians insist (since they, too, cannot tolerate the concept of familial retardation), or the product of some kind of deprivation, simply does not strike me as being the whole picture. I am quite willing to entertain the possibility that the population constitutes a genetic pool, and that, given that pool, there are going to be variations in intelligence, regardless of the experiential phenomena encountered by the child.

An approach about which the geneticists seem very confident, but one that has not had

its proper impact on the area of social deprivation, is that involving polygenic models of intelligence. These models very nicely handle the distribution of intelligence, at least within the IQ range of 50 to 150. This approach, which is of course more complex than the old genetic viewpoints of intelligence, strikes me as perfectly adequate to explain the human variability in intelligence almost independent of experiential phenomena. These polygenic models are almost never mentioned by people in the area of social deprivation when they attempt to come to grips with the problem of how experience influences intelligence.

It is not my purpose here to assert that experience is unimportant. Obviously it is important. What I am saying is that it certainly does not operate as simply as the majority of workers in the area of social deprivation would have us believe. In my estimation, just how cognitive development comes about is still one of the important unanswered questions in psychology.

My purpose here is to sound a warning—a warning highlighted by a quotation from another philosopher, a more contemporary one. I think it was Santayana who said that those who do not know history are forced to relive it. It is interesting to me that many workers who have suggested exactly what to do with socially deprived children in order to increase their cognitive ability, or how to move them from stage to stage in the Piagetian sense, do not seem to realize that exactly this kind of effort was made in this country at the turn of the century and later. It was then that Itard, Fernald, and others were swept up by the mental orthopedics notion advanced by none other than Binet. The notion was that if a child is cognitively inadequate, there are a variety of sensory and learning exercises that would correct the deficit. Some of these practices were very imaginative, and some are just being rediscovered today in the enrichment programs found throughout the country.

That was an optimistic period, when every child was going to become normal in intellect

through the use of certain experiential interventions. Unfortunately, even after these Herculean interventions, not much happened. The retardates were still retardates, and at that point it was decided that absolutely nothing could be done for these children. It was then that the history of the retarded in this country entered its darkest phase, with the children simply being left to vegetate in huge state schools.

I am saying that overemphasizing the role of experience and the amelioration that can be brought about through experiential intervention will, in my estimation, lead to disappointment. This kind of overoptimism will inevitably breed undue pessimism.

A recurring problem in the social deprivation area has been a tendency on the part of workers to rely too heavily upon very gross measures of cognition. I have in mind our IQ measures, which many mistakenly feel to be an inexorable reflection of cognitive structures. The belief is widely held that a change demonstrated in the intelligence quotient is a change demonstrated in cognitive development. This is hardly the case. I should like to share with you an impression gained in my travels around the country looking at centers in Operation Head Start, which is an effort to give some six hundred thousand children of the poor various experiences this summer that will help them in their school work when fall comes. I have been astounded by the fact that no matter what kind of program they are subjected to—and the programs vary greatly, some being very authoritarian, some very open, some emphasizing sensory training, others emphasizing tender loving care—most of the children show an increase in intelligence quotient.

I was very much amused to learn that one of the centers reported IQ increases averaging a point a month. Certainly the data do indicate that if you put a child in this particular program for ten months, his IQ is likely to rise by about ten points. The unquestioned assumption was that this increase reflected a

change in the formal level of intellectual functioning.

We have to remember that the intelligence quotient does not reflect total cognitive functioning in any formal sense. It actually does reflect some formal cognitive processes, but it also reflects achievements and motivational factors such as attitudes, values, and defenses.

In a project in New Haven, we decided to see whether we could discover how much of such changes are truly intellectual in nature and how much motivational. We tested children in two different ways. The first procedure involved administering the Stanford-Binet in the standard manner. With such a procedure disadvantaged children often respond with "I don't know" and other indications of reticence. A week later we tested the children again, this time using what we call an optimizing test. In this procedure we were very warm and supportive toward the child. If he said, "I don't know," we said, "Oh, come on, you know that." If he failed an item even after urging, he was given an easier item. Lo and behold, what we discovered was a ten-point increase in the IQ within one week!

Now, it is ridiculous to say that one week of training has raised the IQ by ten points. The study does suggest what may be happening in enrichment programs. These kinds of experiential interventions probably do not change the child's intellectual structure but rather his motivational structure. What should be emphasized is that such a change is just as important, in terms of social competence, as a change in the intellect itself. It may be that after ten months in this particular nursery school, what has been produced is a child able to utilize all the intellect he has, which is an important finding and certainly bodes well for the child and for society. However, there is a basic practical issue in all this. If the changes produced are cognitive in nature, then emphasis should be on sensory training and the sorts of things that are logically related to the formal processes that go to make up intellect. If

the changes are actually motivational, we will want to do something quite different with the child.

Without going into a great deal of detail about my own work, I should like to tell you my conclusion after some years of effort: that there is less plasticity to intellectual development than most contemporary theorists in America would have us believe. One cannot move children from one cognitive level to the next with the ease suggested by the Bruners and the McVickers Hunts. I do think, however, that there are important organismic systems other than cognitive ones. Physiological people have been tremendously concerned with cognitive development, and rightly so. But cognition and the formal processes that constitute it are certainly not all there is to development, to social competence, or to functioning in our society. It strikes me that the motivational system is equally important, and yet there has not been the same kind of point-to-point mapping of motivational systems. For instance, to give a very gross example, it is fashionable to say about deprived children: "Here are five-year-olds who commonly do not know their own names." Where does this come from? Well, you ask the child, "What's your name?" He looks at you and he sometimes says, "I don't know." So then you say that this child has had certain experiences that lead him to be unable to recall or give you his name. In my opinion, this is claptrap. If you take the trouble to really interact with these children, you discover that they do know their names. However, given their value system and their general approach to life, they become apprehensive when somebody asks, "What's your name?", wondering whether the interrogator is a policeman, what he is going to do with the information, and so on. The best gambit is therefore to say, "I don't know."

We seem to have developed the view that the child mediates questions in the same manner as a computer. The stimulus question is presented to the child's cognitive program, and a response comes out that gives you an

unerring indication of the nature of this program—or cognitive schema, depending on which language one likes to use. But that is not the case. There is another system that is just as important in determining whether the child gives you a right answer; it involves his wanting to, his general approach to the questioner, his reward system, and so forth. Thus, the entire intellectual process could be short-circuited by a child's particular value or fear.

It has also been my experience that this motivational system is much more plastic, much more open to experiential effects, than cognitive development but is just as crucial in determining the child's general level of social competence.

My conclusions do not differ drastically from those of Dr. Richardson. Perhaps the difference could be stated like this: Our goal in this country at present has been to get every child to function at some ideal level. In my estimation the appropriate goal is to get every child, whatever his capacity, to optimize his behavior. This goal is not as flashy and in many ways not as exciting, and probably cannot muster as much foundation support, but I think it is more realistic. It is certainly one to which I and my co-workers have given our efforts.

Moderator: Are there other comments, criticisms, expressions of points of view?

Wolman: I should like to direct a question to both Dr. Richardson and Dr. Zigler, because they have been pointing out the difficulties and the great many variables, both in methodology and in conclusion, with respect to cultural deprivation. Is it unfair to ask their reactions to the preceding discussions on nutritional deprivation—what they think of the methodology, conclusions, and the like in that field, which, if it does not have as many variables, certainly has its own quota?

Richardson: Approaching malnutrition (which I deliberately did not touch on) from the standpoint of behavioral science, and from that of a sociologist rather than a psychologist, I believe there are a number of variables

that could profitably be added to the studies. Let me give one or two illustrations.

I think that we have paid relatively little attention to such a simple variable as family composition and family size. Are there certain ordinal positions in the family that are more likely to suffer from malnutrition than others? For example, it was reported last year by Dr. Mile, after an examination of children's growth curves, that slower growth and faltering in growth appeared to be more likely in second and third children and less so in the first and in the fourth and subsequent ones. This finding is very preliminary; it may not be valid. But it does suggest the possibility that during the early development of the second and third child the mother's resources are taxed to the utmost, with no older children able to help. By the fifth or sixth, some of the older children can help with the younger.

Another type of factor that could be very profitably examined is the position occupied by the families in the social structure of the community. In other words, what are the human resources that can be brought to bear in any particular family? I think it is fairly clear that some families are very isolated, and the mother can call on very few people for either material or human resources, whereas other women are part of an extended network of family and friends who have had a long history in the community.

In short, I can see a number of serious factors to be looked at—not separately, but in conjunction with the others—that could add a great deal to some of the studies now going on.

Chagas: Has Dr. Zigler said that behavioral scientists do not accept the polygenic system as an explanation of human diversity, or that they accept it as the sole explanation?

Zigler: It is probably both. There is a reluctance to take such models seriously, because of the experiential bias that characterizes the thinking of workers in the area of social deprivation.

Waterlow: I was much impressed by the point of view put forward by Dr. Zigler. It seems to me that we have to face the fact that these genetic differences tend to be perpetuated or even magnified by the conditions of our society. If I might give a perhaps not-too-serious example from the other end of the scale, I remember reading that it has been shown—I can't tell you how—that the most nubile women, and by nubile I mean beautiful, intelligent, and rich, are the least fertile. The explanation is that women who are not very fertile could not perpetuate their stock unless they had these other advantages.

Moderator: We shall continue the program with a presentation of the dimensions of early experience by Dr. Thompson, of Wesleyan University, Middletown, Connecticut.

PSYCHOSOCIAL AND CULTURAL DEPRIVATION IN PSYCHOBIOLOGICAL DEVELOPMENT: DIMENSIONS OF EARLY EXPERIENCE

William R. Thompson

Those of you who have read the paper by Dr. Holmberg, for whom I am substituting, will appreciate that deprivation is a terrible

thing, whether it has to do with a so-called manor subculture in Peru or a slum in Harlem or, in some slighter degree, any middle-class

home. We have already learned from some of the talks today that it involves both biological and psychological aspects.

What we must discover is exactly where we can break in to apply remedies for these kinds of deprivations. In human beings, the family is a kind of self-perpetuating organization, involving two generations. While it can often be good, it can also be extremely bad. Since it does involve two generations—that is, children and adults—we have to ask ourselves which of these should we be dealing with, and how.

Now, Robert Hess, whom Dr. Richardson quoted, discussed in a recent article the notion of welfare. He suggested that by dealing with deprivation in terms of a "welfare" concept, we may be in fact institutionalizing it rather than removing it; that is to say, we come to designate a class of people as welfare individuals, and by so doing we perpetuate this class of people in the society.

Instead of dealing with the adult in terms of welfare policies, we can attempt to deal with the children of the families concerned. This is, in fact, Hess's major argument. It is this hypothesis that I shall try to develop: that the retarding effects of deprivation are maximal in childhood and that consequently it is on children that we must focus. I think this is the position taken by many people here today, such as Dr. Richardson, Dr. Cravioto, and Dr. Dubos. It is certainly one that I have emphasized. Although it is a fairly reasonable view that early experience is important, more important than later experience, and that young organisms are in a sense more plastic than older organisms, the position is nonetheless shared by everybody.

For example, in his recent address as outgoing president of the Eastern Psychological Association, Dr. David McClelland (1965) of Harvard dealt with this theme. What he has been working on, as many of you know, is the problem of so-called need achievement. He has now geared his research efforts to a very epic level and concerned himself with the

problem of trying to inject need achievement into "underdeveloped" countries—"deprived societies," to use our nomenclature here.

Supposing you can inject need achievement into such societies and make them entrepreneurial and hence successful and happy (which is itself a large assumption), the question arises, At what age do you inject it? Professor McClelland takes the view that you can do this at almost any period of development. As exemplars of this point of view he takes on the one hand the Skinnerians, who say essentially that all you have to do to change an organism is to get it to emit a certain kind of behavior, which you then reinforce or reward, and on the other hand the missionary, who, without any psychological sophistication, goes into a society and—much to the distress of the anthropologists—changes it to his whim.

I myself think that the assumptions of the Skinnerians are wrong. I also think that the missionary succeeds only because he has a mission school, and it is here rather than in the adult culture that he makes changes.

If we abstract from these kinds of generalities, we face the essential question that I have already posed: Can young things be changed or influenced more readily than mature things? In other words, is early experience important?

This last phrase is a very common one. We have discussed it today in many of its aspects. Though seemingly simple, its meaning is actually rather complicated. For example, one part of it concerns the question of what early experience is like. Dr. Richardson and Dr. Zigler have both been concerned with this problem, which is basically a normative one. What are young organisms like at different ages? I think Dr. Zigler will agree that most of child psychology has dealt mainly with this kind of question.

A second set of questions is raised by the second part of the phrase—"is . . . important." This takes us from a normative into a predictive framework. When we say the effects of an experience are "important," we mean that they are large, or long-lasting, or irreversible,

or wide-ranging. We are, that is, concerned with predictive problems. These have belonged traditionally more to psychiatry than to child psychology. It was such questions that were raised by Freud, and since his time the whole psychoanalytic enterprise has been concerned with this question and has tried to explain adult behavior—particularly adult pathological behavior—in terms of events that occurred in early childhood.

Thus, in any kind of model that we develop to deal with the statement "Early environment is important," we have two basic kinds of problems, one normative, the other predictive.

My own involvement in this has a fairly long history. I have been juggling nature and nurture for a fairly long time, and am perfectly willing to operate with either.

At this time, I shall deal mainly with the nurture problem. My interest in it stems from the three years I spent at McGill University, where I spent part of my time working on early experience, which Donald Hebb had emphasized in his book *The Organization of Behavior* (1949). I spent the rest of my time at the Jackson Laboratory in Bar Harbor, where I did research on some basic problems in behavior genetics.

The notion Hebb developed in his two-phase neuropsychological model was that in the early part, or first phase, of development the organism possesses a great deal of plasticity. Once the neural circuitry is set, however, it is difficult to undo it. This emphasis of Hebb's on early experience produced a great deal of research, in one part of which I was involved. Several colleagues and I attacked the problem in a very global way. What we did was to put a group of Scottie puppies in restriction—that is, in isolation cages. Their littermates were farmed out to stimulating Montreal homes where they had everything that a dog could desire. Later on the control animals were brought back to the laboratory and were compared with the restricted experimental dogs on a number of behavioral tests.

As one indignant lady who heard about the

work said, it is very obvious that if you treat an animal in such a fashion it is going to suffer. In some ways this was true of our isolated Scotties. They showed retardation in intelligence. They showed hyperactivity. They showed curious kinds of emotional changes and an unusual epileptiform behavior. But, contrary to expectations, they did not look like unhappy dogs. This fact perhaps did not strike me much until I took part in a symposium arranged by Hoch and Zubin (1955) in New York, where I gave a paper on my dogs immediately before another person—William Goldfarb—who reported on orphanage rearing. The picture he painted of these children, while it agreed in some dimensions with my results in dogs, seemed to disagree in others. My dogs were, as I said, very happy-looking animals. The orphanage children were not particularly happy, but in some other ways were quite like the dogs. This was very puzzling to me and led me eventually to try to develop some kind of schema that could explain apparent contradictions of this kind between the effects of early experience in human and in animal subjects.

During the past few years, in considering this problem, I have tried to work out a model that takes the adult personality as being stratified in terms of developmental events.

What we can consider first is one main dimension of development that I think all biologists agree is related to aging. Age by itself, as Dr. Zigler (1963) and others have pointed out, is an empty variable. Certain things happen with it. One of them is what is called differentiation, a term that has been used a great deal by both biologists and psychologists. What I have done is to take this dimension as an index of perceptual ability on the one hand and what might be called performance on the other. In other words, I have separated out perception and performance, and I have postulated that they develop at different rates.

Now, I do this for a particular purpose. In considering psychological variables, the main ones that have to be dealt with are perception,

performance, and storage. Storage is usually represented, in the nomenclature of behaviorism, as an *S-R connection*. These terms stand for "differentiated stimulus" and "differentiated response," the differentiation being due to development. What I am suggesting is that during development there is a lag of differentiation on the output as compared with the input side.

If one accepts this postulate—and I think it fits common sense as well as a good deal of normative data—one is led to deduce the existence of age zones. In the first, both input and output are undifferentiated. In the second, where the input differentiation is rising sharply, there is a relatively high degree of differentiation on the input side but still a rather low degree of differentiation on the output side. In the third, there is relatively high differentiation on both sides of the organism.

The complete formula commonly used to explain complex behavior—perhaps a meager one for human learning, but at least appropriate for a good deal of complex animal learning—consists of these components: unconditional stimulus, unconditional response (salivation to meat, startle to an arousal stimulus, and so on), conditioned stimulus (that is, a signal or a cue), and conditioned or instrumental response.

At maturity, all components are present—the US, the UR, the CS, and the CR. Going back to what I call the second age zone, one—the CR—has to be subtracted by definition, so that only US-UR and CS are left. Going back still further in development, the CS must by definition be subtracted, since it is a signal that is differentiated out from the rest of the environment—which, by the assumption I have made, is impossible at the first age level. So at this level all that is left is a US-UR relationship. What I am suggesting, then, is that different kinds of storage mechanisms operate at different ages and that these storage mechanisms are given by three different types of learning.

In the first age zone, when there are simply

a US and a UR—that is, some kind of arousing stimulus and, in response to it, a change in arousal level—the only way the organism can change is by what can be called non-specific habituation. Repeated stimulation of the young organism produces alterations in general arousal level.

In the second age zone, the organism acquires the ability to differentiate out cues. It can still be aroused, but the arousal can now become attached to some specific object—for example, a mother, or a father, or a dog, or a specific food, or any other section of the world. At this age, storage occurs maximally by Pavlovian classical conditioning, or if you like, emotional learning, in which emotional responsiveness becomes attached to some part of the world that has been differentiated out in perception.

In the third age zone, articulated performance becomes possible. Now there is the possibility of an organism's doing something about any classically conditioned relationship previously acquired. A child can be afraid of a dog, but he can also now run away from it, shoo it away, or take all sorts of other complicated steps to circumvent meeting dogs or things like them.

In summary, the schema outlined provides for three age zones during each of which there is a relative dominance of a certain kind of storage mechanism. Let us now look at some of the data bearing on this.

It is a fact—and this is why I brought up, in connection with Dr. Widdowson's paper, the effects of crowding and its possible residues—that very simple treatments can be imposed on young animals that will produce in them radical and long-lasting changes. For example, it is well known that if infant rats between the ages of one and twenty days are taken out of their home cage, placed in a box for thirty seconds or so, and then returned, very large differences can later—say at sixty or ninety days—be found between these manipulated animals and animals that have not been touched (Denenberg, 1962). This is the effect of non-

specific stimulation, since almost any kind of treatment will work. It was initially thought that being nice to the young rats was essential; hence the term *gentling* was used to describe the treatment. But it is known now that the same effects can be produced by means of procedures that certainly do not involve being gentle, like shocking or vibrating, throwing the animals up in the air, compressing them, heating them up, cooling them down, and so forth. The type of treatment, in other words, does not matter; a Spartan treatment at this age will apparently have just about the same effect as a loving treatment, depending on the intensity of each. You can overdo gentling as well as shocking; too much love will have just as noxious effects as too much hate. These terms—*love* and *hate*—are, in a sense, irrelevant at this stage of development.

The kinds of changes that are produced during this zone have to do mainly with what might be called temperament, in the sense that they are global and nonspecific; for example, the behavior of a rat in an open field, its activity level, its timidity, physiological changes (as in adrenal size), and changes in general rates of growth and development. They all have to do with general arousal level, and they are produced by general massive stimulation.

At the human level we find some analogies to the animal data. A recent study by Whiting and Landauer (1963) exemplifies this. They dealt with a number of cultures that use so-called scarification practices like circumcision and putting scars on the face, in bringing up children, sometimes for cosmetic reasons and sometimes for religious reasons. Using the Yale Human Relations Area File, the authors located a number of cultures that did not use such practices. They then compared the two with respect to bodily size. Genetic, nutritional, and climatic factors seem to have been adequately controlled. The outcome was that those that did use such practices were found to be taller than those that did not. This result fits in very nicely with the animal data,

and so I should certainly be quite prepared to believe in the possibility of this kind of effect.

In the second zone, when perception of a stimulus becomes possible, emotion or arousal can now become attached to some particular thing. Again we have evidence. For example, in the mouse, it seems to have been shown that classical conditioning is maximal at around twenty-five days of age (Denenberg, 1958); it is less easily instituted before and after this time. In human beings, according to the psychoanalytic model, the exigencies of the Oedipal situation occur between four and six years, and these mainly where they involve the affective attachment between a child and a parent or some parent-surrogate. The same applies to chicks, in which imprinting occurs at a certain critical period about twelve to fourteen hours after birth (Hess, 1959).

I call this an affective meaning zone, since the world at this time must take on affective meaning but not yet meaning in terms of the coping responses to it, which have still to be learned.

The third age zone comes when a child begins to lock into the culture—to become, in a sense, an adult who can do things, think intelligently, and deal with reality. The transition from one to the other is, I think, a very important time. It must occur during the pre-school period, around five, six, or seven, at which time, as many child psychologists have noted, there is a very distinct kind of shift, sometimes called the seven-year-old shift. The child turns from being only a child to becoming partially an adult.

This is my schema, in a very capsulated form, to describe the *nature* of early experience. It does not, of course, deal with the problem of *importance* which has to do with another kind of dimension. I have a faith that importance, in terms of magnitude of effect, is inversely related to age. There is certainly a good deal of evidence to suggest this, but it is very far from complete.

The model suggests that the adult can be

considered to be stratified in terms of the residua of events occurring during the three zones of his development. As Dr. Zigler has already emphasized, genetic factors also play a large part. Much of a genotype simply determines the modal level of a trait—for example, what level of intelligence an individual is likely to have. But there is another sector of genetic influence that is most important in the context of this discussion. This has to do with plasticity, or buffering; that is, the degree to which an individual genotype is buffered, in general and also at different specific ages. I described before some effects produced in rats by early handling. These occur readily in laboratory rats. Wild brown rats, on the other hand, show little change when subjected to the same procedures. They do not become tamer, but remain just as wild. Another example has to do with imprinting. In certain gallinaceous species, early exposure of the young bird to some older counterpart produces later following, and this supposedly has some advantage *vis-à-vis* mating choice, since the animal selects as a mate one of the class of animals on which it was first imprinted. There is some evidence that this is true.

As it turns out, nature is, as it were, "lazy" for some species: it has not allowed for the introduction into the situation of people like zoologists and psychologists, who come along and permit these birds to become imprinted on very strange kinds of things, such as stovepipes, Coca-Cola bottles, wooden decoys, or themselves. This obviously causes a problem in regard to reproductive behavior. In one sense, such birds are rather poorly buffered, inasmuch as their genotypes do not fix a narrow range of objects on which they can be

imprinted and with which they later prefer to mate.

On the other hand, some parasitic birds have adapted quite differently. The cuckoo may lay its eggs in the nest of a meadow pipit, but the young cuckoo does not later mate with the meadow pipit; it mates with its own kind. So it is apparently not imprinted on its foster mother. It does appear, though, from some evidence I have heard of secondhand, that it is imprinted on the nest, and when it grows up it will lay its eggs in the type of nest in which it grew up. Thus there is a great deal of rather interesting variation in respect to the way an organism is buffered and the kind of things against which it is or is not buffered.

To summarize, early experience is dimensional or zoned, and the events occurring during each zone will essentially determine the structure of adult personality. If we find in our society adults whose attributes are not synchronized with the general social good, then we can best direct our remedial procedures to the zones of early experience from which these undesirable attributes derive. The adult is too intractable to change; whatever social welfare practices may be instituted to deal with the problem at this level may have a temporary usefulness, but will surely not provide a final solution.

Moderator: It seems to me that Dr. Richardson's, Dr. Zigler's, and Dr. Thompson's papers have presented three complementary and supplementary points of view.

I should now like to ask Dr. Birch, of the Albert Einstein College of Medicine, New York City, to speak on the more general subject of "Research Needs and Opportunities in Latin America for Studying Deprivation in Psychobiological Development."

RESEARCH NEEDS AND OPPORTUNITIES IN LATIN AMERICA FOR STUDYING DEPRIVATION IN PSYCHOBIOLOGICAL DEVELOPMENT

Herbert G. Birch

After listening to Dr. Thompson, I don't know whether I am a cuckoo, a goatsucker, a cowbird, or a meadow lark in approaching this problem, because my imprinting is not entirely clear. Having prepared these remarks in advance, I now find that in part my assignment consists of considering what other people have said here about research needs and opportunities. Given these polygenic influences, I shall try to produce a hybrid structure, if I may.

What has impressed me most today is the privilege of having participated in a discussion of mechanisms and forces affecting psychobiological development that has been unique in a number of ways. It has had the dual property of being very broad in scope and at the same time intensive in the consideration of certain problems and issues. If I view my own assigned role in the proceedings as a modest one—that of translating certain of the broad general issues into a more clearly defined set of problems particularly pertinent to research in Latin America—I think that the first task with which I am confronted is that of delineating certain of these issues more sharply.

It is necessary to recognize from the very beginning of such a discussion that identifying pertinent research problems and needs is a quite different task from identifying research opportunities. In a sense, this distinction is not unlike the one made in economics between desire and demand, with the latter defined as the former backed by the ability to pay. In research, a problem becomes an opportunity only when the appropriate research circumstances—including especially advantageous situations, adequate laboratories, and,

above all, highly skilled and excellently trained research workers—are available and ready for application to the problems at issue. In their absence, a research problem may well exist, but certainly not a research opportunity. However, these are logistical considerations, which, though of great practical importance, are perhaps better deferred for a separate discussion. For today it may perhaps be more appropriate to retain as our focus not so much the identification of opportunities in the sense that I have just considered them but rather the identification of issues and therefore of *potential* opportunities.

The papers presented at the meeting, and also our general information on psychobiological development, suggest that an understanding of psychobiology as a developmental process depends on an understanding of at least two sets of forces and their interaction. The first of these is the organism and its physical and functional integrity; the second, the conditions of life and experience, both intimately personal and broadly social, to which this growing organism is exposed.

In this interrelation we have the circumstances that define the organism's competence and individuality. Neither body of knowledge is in itself sufficient for an understanding of the developmental process. Abundant evidence exists from investigations both of lower animals and of children to indicate that psychobiological characteristics can be modified in significant ways, both by structural changes in the nervous system and by variations in the opportunity to have had past experiences of a certain kind at appropriate stages in development. Moreover, neither set of events operates in isolation or in independence of the other,

since structural change modifies the effective environment from which the organism is capable of gaining its experience.

Thus, for example, for bats an effective environment includes vibratory stimulations of 50,000 cycles per second. These do not constitute features of my effective environment, although they are objectively present. Similarly, ants can very readily be observed if we place red-glass covers over the nest. The light in this circumstance is outside the visual spectrum of the ant, but is well within our own, and so we can see the ants functioning "in the dark."

If we recognize a difference between objective situation and environment, then we appreciate that initial differences, whether in temperamental organization, in range of responsiveness, or in integrity of the nervous system, represent a primary basis for the construction of quite different environments out of identical surrounding conditions of life.

These differences in initial selectivity and in the organization of the objective conditions may serve either to exaggerate or to minimize the consequences of potential alterations in the developmental course that may derive from a modified nervous-system structure. For example, we know from clinical situations that there are certain varieties of children with primary damage to the nervous system whose functioning grows increasingly disorganized in an unstructured and unreplicative environment. Whereas if they are provided with a repetitive routine, a monotonous and repeated structure, fundamental positive alterations in behavior style may in fact occur.

Thus, a primary condition of structural or physiological alteration in the central nervous system does not in and of itself produce symptoms. Rather, symptoms are the result of interaction with specific and organized conditions of environment.

If, then, one focuses upon malnutrition as a contributor to inadequate development of the central nervous system, it becomes clear that the condition of nutritional risk is most likely

to occur in children whose general environment is often considered to be suboptimal for the acquisition of certain kinds of skills, attitudes, manners, values, functions. These environments are frequently characterized by poverty, educational limitation, and cultural restriction. Considerations of this kind have led Coursin, for example, in a recent review of the effects of undernutrition on the functioning of the central nervous system, to suggest three areas of investigation as having "enormous significance for study." It is remarkable how closely the issues he identifies resemble certain aspects of the program of presentations here today. They are as follows:

1. The exploration of molecular components operant in brain cell as they relate to mentation.
2. The development of more meaningful procedures for measuring brain function on a conceptual basis with consideration of family background, environmental circumstances, and cultural facts.
3. Devising better techniques for measuring the neurophysiological mechanisms that integrate them both into total functioning complex of the individual.

Let us turn first to a consideration of the integrity of the central nervous system itself. I think it is apparent that the children with whom we are concerned are at multiple risk of sustaining pathological alterations in their nervous systems. There is little reason to assume, given the conditions surrounding the pregnancies of which they are the products, that at birth these are children without a high prevalence of damage and of potential defect. The facts of birth weight and motor precocity do not in themselves constitute decisive evidence of the integrity of the central nervous system. It is even possible that some aspects of so-called motoric advance reflect pseudo-precocity associated with brain damage. Motor precocity, which disappears and has little relation to the later, more complex integrations of directed motor functioning, is a problem that in itself is very well worth investigating.

The epidemiological findings of Dougal Baird, on children born to stunted mothers who have had marginal levels of nutrition and

hygiene during pregnancy and suboptimal management during labor and delivery, leave little reason for assuming that such children are not at considerable exposure to events and conditions that may result in primary damage to the nervous system.

I think that we have the responsibility of looking with a somewhat jaundiced eye, if I may use a neonatal phrase, at the reports of fifteen or more years ago that suggest that, even if the mother's nutrition is not what it should be, the fetus is really a perfect parasite and lives quite well in his environment. In large part these reports depended upon altogether inadequate estimates of neonatal status and function, and provide no evidence that warrants this kind of conclusion. Further, evidence on animals, including that presented by Dr. Widdowson today, suggests that when animal mothers are deprived of certain essential components of diet during the course of pregnancy and weaning, the development of the offspring is affected.

Our current knowledge of the functional level of neonates and very young infants in Latin America must be recognized as being fragmentary. Most of our data consist of incomplete information on weight, body length, and body proportion based on inadequately defined populations and population samples. Both the need and the opportunity exist to apply currently developing and advanced techniques, ranging from careful assessment of neural behavior to electrophysiological evaluations in infancy, to populations of children who are likely to be subjected later to nutritional and associated risk. This means, of course, field study and community study as contrasted with convenient dependence on hospital populations, which are close to the site of the investigator's laboratory but cannot be defined either as samples of specific populations or as representative of children at risk.

Numerous studies have identified exposure to severe nutritional risk as being most likely in the period following weaning. When undernutrition does take place in this period,

it can have both direct effects on the central nervous system, which is growing and differentiating at a rapid rate, and indirect consequences for psychobiological development by reducing or otherwise modifying the child's responsiveness to his environment. This latter risk is particularly cogent if we recognize that the phenomenon of apathy in malnutrition is marked and occurs during a period in which a variety of experiences may be critical for determining the organization of psychobiological functioning for subsequent learning. It may be that if a child is unresponsive during certain of the periods to which Dr. Thompson has referred, he will never again have a similar opportunity for achieving a necessary organization, and that deprivation at specific points may have quite disastrous effects not merely because of its direct action upon the nervous system but also because it insulates the organism from necessary aspects of environmental stimulation and experience. Furthermore, when undernutrition accompanies weaning, it is not infrequently associated with changes in child care involving an often abrupt transfer of responsibility from the mother to other members of the household or of the community.

Each of these phenomena—the direct and indirect influences of undernutrition on the growth and organization of the central nervous system, the effects of malnutrition on responsiveness during critical periods of psychological development, and the effects of change in the child's care in association with his exposure to nutritional risk—represents an area of inquiry most worthy of being studied.

Over the past decade a considerable body of evidence has been obtained through studies of children, particularly in Latin America and in Africa, to indicate that significant degrees of malnutrition experienced during the first years of life are associated with retardation in mental development. Such retardation, though often mild, is of sufficient magnitude, it has been suggested, to result in educational difficulties and limitation in general adaptive capacity. The specific alterations in nervous

system structure that underlie these functional changes are as yet very incompletely understood. Relevant animal experimentation has been crude and has only begun. It is primarily of value in suggesting areas that are worthy of further intensive inquiry, rather than in providing us with answers for our problems.

It is well known that for normal development the nervous system must incorporate lipids, amino acids, and a variety of other substances, the available quantity and quality of which may be inadequate in the malnourished individual. However, we still need to know much more precisely the amounts required. We must know the relation of these needs to general requirements for growth, the degree to which general caloric inadequacies or conditions of health may result in the appropriation of essential substances for energy production rather than for biosynthesis, and the temporal sequence in which the metabolic precursors resulting in the most favorable rates of nervous-system growth and development must be available.

Clearly, the answers to such questions can best be obtained by laboratory investigations in which neurophysiological and neuroanatomic investigation is combined with detailed studies of nutrition, biochemistry, and biophysics. However such studies do not provide us with direct information on psychobiological development, because there is no simple, direct relationship that I know of between behavioral adequacy or intellectual capacity and any specific detail of structural integrity. To understand the functional consequences to behavior of various types of structural and biochemical aberration in the central nervous system is a problem in itself. It is necessary to study behavior in order to answer this question, and to define the behavioral demands that are being made. Thus a program of behavioral study using sensitive methods of behavioral assessment must be linked with structural and physiological investigations if the pertinence of their findings for psychobiology is to be determined rather than merely inferred or assumed.

Evidence has been accumulating, too, that suggests the possibility that undernutrition may place the developing central nervous system at risk in certain indirect ways. One finding of particular interest to me is that mechanisms of immune response may be markedly interfered with in malnourished organisms. If these findings are sustained in further investigation, the possibility exists that the nervous system of the malnourished child who has a suppressed immune response may be more readily affected by infection or its attendant sequelae than would be the case if he were adequately nourished. I know of no evidence on this specific question, but I think that the evidence already in existence makes it one worth studying.

Thus infection, which we have already considered as a potential contributor to and a synergistic phenomenon in malnutrition, may also affect the malnourished child in a manner that directly places the central nervous system at greater risk.

Most of the kinds of studies I have just mentioned, though directly pertinent to health problems in Latin America, are of course not by any means those for which Latin America provides either special facilities or unique opportunities. Clearly, they are important to Latin America; but such investigations, and many others in biology and chemistry and behavior as well, may be pursued in any region and derive no special value from the place in which they happen to have been conducted, whether this is North America, Scandinavia, or anywhere else.

What, then, are some of the special opportunities for research in the relation of deprivation to psychobiological development in Latin America? I should like to consider this issue briefly.

In the main, I think, the special opportunities existing in Latin America for the study of the relation between psychobiological development and deprivation derive from the social conditions of life there. Because of these conditions, unique opportunities exist for the study of deprivation in both the biological and the social

aspects in human populations—regrettably, in a sense, since the opportunities derive from social dislocation and from what in a real sense is human tragedy. However, it is present, and it affords an opportunity for investigations that have the twofold virtue of being important for our understanding and of being in the interests of the people studied.

Given the diversity of settings in which children are variously subjected to nutritional deprivation at different ages, to all sorts of patterns of care, to numerous differences in values, attitudes, and personal and social motivations, the opportunity clearly exists to delineate, through carefully conducted ecological and cross-cultural inquiries, the patterns of circumstances resulting in significant degrees of deprivation that interfere with normal psychobiological development. Further, it becomes possible, with appropriate research designs, to delineate the consequences of such deprivation when it has occurred at different points in the child's life and within the matrix of different familial, social, and cultural settings. Clearly, such inquiries should be longitudinal for certain kinds of investigation and for certain kinds of problems, cross-sectional for others, semi-longitudinal in still others. The design of the studies would depend upon the problem and the opportunities for its investigation.

Perhaps the first question that such studies can answer is the critical one raised repeatedly in today's discussion: the relation between the time in the child's life at which a given event has occurred and the consequences of the experience for his development. Preliminary evidence that has accumulated in clinical settings suggests that nutritional deprivation during the first six months of life may be most significant in interfering with later psychobiological development. If this is in fact true, and is sustained, then a most interesting research opportunity exists precisely because there is fairly good evidence that institutionalization, deprivations of stimulation, deprivations of maternal care, during the first six months of life, have relatively little effect on the subsequent develop-

mental course. One may have an experiment in nature, then, that permits of isolation of the nutrition element from the general circumstances of care and so enables us to define more clearly the causal relations between nutrition and later disturbances.

A second opportunity, I think, is that of looking at nutritional deprivation from the standpoint of whether it is or is not associated with alterations in maternal care pattern. Communities could certainly be found in which there is nutritional deprivation that is not necessarily accompanied by a shift from an intimate relation with the parent to a mere vagrant pattern of substitute care. The comparative investigation of consequences in these two sets of circumstances would provide an excellent opportunity for further delineating interactions among significant variables and for determining their influence on the developmental factor with which we are concerned.

A third question that emerges out of much of the discussion, and that arises again and again in the anthropological as well as the medical literature on nutritional deprivation in Latin America, is whether malnutrition is the product of an objective lack of nutrients or of improper administration of nutrients as a part of a policy of child-rearing. The mythology of nutrition in a number of subcultures is itself a fascinating problem for social research as it relates to the effects of attitudes and of pre-scientific and often pre-logical notions about health and nutrition on the care and management of children. Pursuing, for example, the primitive magic of hot and cold types of food and of weak and strong foods, one being good for one type of individual and another for another, one may make it possible to find an extension of these notions to the care of the child. If he is viewed as weak and therefore capable of accepting only weak food, such as *atole* or any of a variety of weak carbohydrate gruels, what occurs has all the properties of a self-fulfilling health prophecy, because a child fed these things does indeed exhibit weakness. Therefore, from the point of view of pre-logical analysis, it follows that he

should now receive weaker foods still; the pattern then established, the attitudes and beliefs, the strongly held notions of what is correct and what is incorrect in age-specific nutrition for children, become problems for public health investigation that are uniquely capable of being investigated in these communities.

Attitudes toward parasitic infestations, for example, are another area in which the evidence is fragmentary, but Cravioto, among others, has reported that worm infestations are viewed not as invasions but as prerequisite to the next stage of nutrition—unless you have certain kinds of worms, you cannot eat certain kinds of foods. Apparently your worms only give you trouble, it is suggested, if you don't feed them right.

These patterns of attitudes and of belief, which interact not with famine but with marginal conditions of nutritional adequacy, involve an interrelation of social and psychological circumstances in the community that have the biological consequence of relatively widespread undernutrition. They deserve very careful and detailed study, because we will probably not be effective in changing practices and policies unless we have a fuller understanding of what it is we are attempting to change.

The association of deprivation with infectious diseases, with a variety of gastrointestinal disorders, and so forth, raises a whole series of problems. Then there are the opportunities for long-term follow-up, which has not yet been done, of people who have experienced malnutrition of varying degrees in early life, and an understanding of the longitudinal course of the changes in functioning that such deprivation may introduce.

If we proceed further, we can identify a vast number of problems in these areas, particularly as they interrelate social organization, population characteristics, nutritional circumstances, and the developmental demands that a society makes upon its population. Unique opportunities exist for such research in Latin America—opportunities that do not exist in many of the industrially more developed communities

in the world.

If, then, my remarks have any function, it may be that of identifying at least a few of the many areas of general pertinence to our issue for which unique opportunities exist in a given geographic area and social region.

Chagas: I should like to call Dr. Birch's attention to some very important factors that have been disclosed in the course of some research projects conducted under the auspices of the Institute of Biophysics of the University of Brazil. An enormous amount of collateral material on populations has already been gathered.

Our first project, some five years ago, dealt with populations in the backlands of Brazil. The second, three years later, was on Chagas' disease, cretinism, and goiter. More recently, two other projects have been started and developed: one, in the State of Mato Grosso, again dealing with cretinism, goiter, and Chagas' disease; the other covering two areas with a radiation background.

The Mato Grosso project may be especially important with respect to the problem we have been discussing. It was undertaken by a group of researchers directed by Dr. L. C. Lobo. Physicians and geneticists worked together in the group, but it was unfortunately impossible to have sociologists and anthropologists joining them. Even so, some very rewarding results have been obtained. Nearly twelve hundred people have already been examined. The area in which they live is rather poor; nutrition is bad and medical care practically non-existent; the population is highly inbred. Among other interesting things, Dr. Lobo has already discovered that the majority of people affected with cretinism do not show any important iodine deficiency; at least, their thyroid function is fairly normal. I should also like to mention the question of the genetic load of lethal genes due to inbreeding, as compared with outbreeding populations.

Of course, the factors of deprivation that can be detected in the most objective way should always be given very special attention in the surveys. This is just to agree with the particular

emphasis on Latin American problems that has been given at this meeting.

Caldeyro-Barcia: There is one very simple problem that may have wide and important implications and is highly applicable to the American continent: the position in which women have labor. In all the Indian cultures in America labor takes place in a squatting position; the supine position comes from Europe.

Physiological studies made at our institution in the past five years have shown that the supine position is most unphysiological, resulting in severe hemodynamics and respiratory disturbances for the mother, and in metabolic acidosis of the fetus, which leads to brain damage. All these troubles are corrected just by changing the position to the squatting position in which the Indians of America, both North and South, have labor. This subject, I suggest, could be taken into account for future research by PAHO.

The National Institute of Neurological Diseases and Blindness has found that in fifteen university hospitals in the United States the incidence of brain damage in one-year-old children is about 2 per cent, which means that several million United States citizens have this damage. In Uruguay it has been estimated at 5 per cent. Western civilization has changed a physiological function into a surgical procedure, completely artificial, and in the opinion of many people the over-all result has not been improved. I think that this problem is particularly pertinent for this hemisphere, in which only half of the population is Western in culture and the other half still follows the old Indian system.

Richardson: I have some brief comments on the results of the collaborative study of the National Institute of Neurological Diseases and Blindness. The early estimates of what types of damage would be expected have been greatly exceeded in almost all cases. I think that the reason is that these studies are in no way representative of the population of the United States at large but rather of the cases that come to teaching hospitals, which have careful screening procedures and tend to obtain the higher-risk

cases. I therefore believe that we should be very cautious in attempting to generalize from the figures of the NINDB study, because they are probably considerably higher than for a population in general.

Chagas: Dr. Caldeyro-Barcia's curious remarks suggest again, in a way, the urgent need for a thorough study of the special problems of human physiology in Latin Americans, especially those living in the tropical regions. We actually know very little about these important problems, Dr. Huertado's remarkable work on the subject being rather an exception.

Is it not inappropriate, for instance, that physicians all over the warmest and most humid areas of Brazil and Latin America in general should be using the DuBois Calorie Tables—which were established for people living in Philadelphia under profoundly different conditions—without previously testing their adequacy to the tropical environment?

Another important question is that of dress. I have been striving in Brazil for a change in our ways of dressing, which should of course be more compatible with the climate of the country, and in general more independent of European and North American standards.

As Dr. Caldeyro-Barcia has remarked, some habits of the ancient native populations may be altogether more adequate, from a physiological point of view, than most of those imported from distant countries with a different climate.

Roche: I should like to comment on Dr. Holmberg's paper on Vicos, in the Peruvian Andes.* I believe that this sort of anthropological study is very germane to an understanding of the "whys" of certain social and political reactions in our countries, although it is certainly an extreme case. I believe it was Simón Bolívar who said that every country has the government it deserves. This sort of study throws some light on the word *deserves* and may help in some interesting political prophylaxis. I vote for the Organization's supporting more such research.

Horwitz: In political terms, the problem is

* This paper was scheduled but was not presented owing to the absence of Dr. Holmberg.

certainly not within our jurisdiction. But I remember Dr. Dubos' pointing out, in our discussions last year, this situation of the rural communities and the migration of populations to the cities. From that we went on to the shanty towns that are increasing so much in Latin America. We are in general interested in improving the conditions of the rural communities, and we have seen during the past year that in many countries the moment that rural groups are properly motivated—that is, as soon as they find that the motivator is sincere—their response is surprising. This has happened when we were working with the governments to install water systems, for instance, or to improve nutrition or to stimulate the people to work on whatever they may choose for the good of their own communities.

So far as the approach to these communities is to improve their health care and their welfare, certainly we are very much involved, and we want to be. We proposed the creation of a Special Fund for Rural Welfare. Unfortunately this idea has not yet crystallized—because of misunderstandings, in my opinion—but we are planning to pursue it because we are absolutely convinced today, after a year of dealing with several different rural communities in Latin America, that the people are waiting to be stimulated to active participation in improving their lot. I believe that this is a beautiful field for any sort of research you would like to do.

Payne: I should like to say how fascinated I have been by the presentations today and to thank those who have taken this trouble, because I have learned a great deal. I heard in a lecture some time ago of a study—I am sorry I cannot say where it was published or give the name of the man—of binovular twins of the same sex, in which it was found that the size of the twin was directly proportional to the size of the placenta. In other words, this was a question of intrauterine starvation. The interesting thing to me was that, after birth, the twins gained weight at the same rate but the "runt" did not catch up with the other; he remained small. My impression is that the impor-

ance of the intrauterine environment has perhaps not been sufficiently stressed here.

Waterlow: What I have to say relates a little to Dr. Chagas's point about the need for more physiological work. One of the great problems in many places, I think, is the question of work output. Many people complain of poor productivity in tropical countries, and we do not know whether the reason is physiological or psychological.

In a study in Jamaica on the output of sugarcane cutters, which is something that can easily be measured accurately, it was found that those who had a poor output had the lowest food intake. This seemed very straightforward from a nutritional point of view, but the next step was to show that the men who had poor food intake tended to be unmarried. The ones who ate well had wives who looked after them. After that comes the fact that in Jamaica you don't get married unless you are a solid citizen who is prepared to work hard and take on responsibility. This is just an example of the usual complicated multi-factor situation. It is the same, of course, for the deprived child.

Many of us feel the need of advice on the best way to tackle such problems and on how to break the vicious cycle. I do not know what kind of people are competent or willing to help in this kind of work. It is a question of experimental design and experimental analysis. I think Dr. Cravioto and Dr. Béhar both have extremely good experimental designs in their survey work. I had rather hoped that we might hear a little more about this aspect of the study of the complicated cultural and psychological factors involved in the problems.

Moderator: I am afraid that this is not the ideal time for that. In fact, I think we must now bring our session to a close.

I know that all of us on the Committee and the staff have felt this to be an exceedingly informative and stimulating day. We all wish to thank each of the speakers for the excellence of his or her presentation and also to congratulate Dr. Martins da Silva and Dr. Allen for the outstanding program they have arranged.

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