Comparative Study of Somatic Stability in Severe Malnutrition and Prematurity

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Severely malnourished and premature infants have in common [i] a high mortality rate from infectious diseases, and [ii] a lack of stability in the regulation of certain physiological constants.

It has been attempted to compare the physiology of premature and malnourished infants. The similarities and differences disclosed in this way may further the understanding of the physiological basis of instability and the high mortality rate in both conditions.

The prematures studied were 1 to 5 days old. Their birth weight ranged between 1000 and 1800 g. The malnourished infants were 3 months of age, all of them severe cases of the non-oedematous type. They were about 30 per cent underweight as compared to normal babies of the same length, and 40 per cent underweight for their age. The wasting thus attained a degree comparable to that of the victims of concentration camps.

This severest type of malnutrition, disappearing in the last years from hospitals, has been known as "athrepsia" in classical paediatrics. It should be emphasized that most of the clinical and physiological characteristics reported here are valid only for this extreme type of marasmus. Malnutrition of lesser severity is distinguished by greater somatic stability. Kwashiorkor, however, though an oedematous type of malnutrition, may have certain features in common with the condition discussed.

Mortality Rate of Specific Diarrhoea

Some *immunological aspects* of somatic stability present analogies between the two groups of infants. There are diseases contagious only to malnourished and premature infants; interstitial plasma-cellular pneumonia may be cited as an example, that malignant and highly infectious disease causing severe hospital endemics in many countries. On the other hand, the *course and prognosis* of common infectious diseases are likely to take a bad turn in both prematures and malnourished infants.

Fig. 1 shows the bearing of age and nutrition, respectively, on the mortality rate of specific diarrhoea caused by *E. coli* B_4 infections. Every

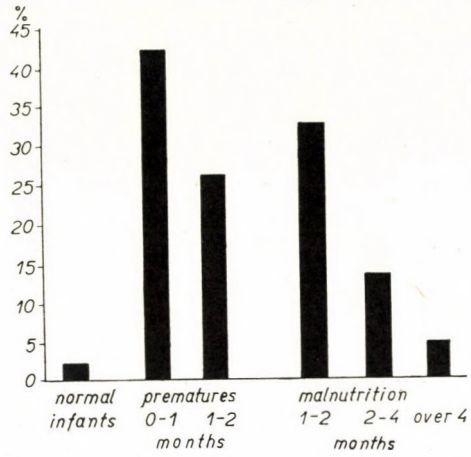

FIG. 1

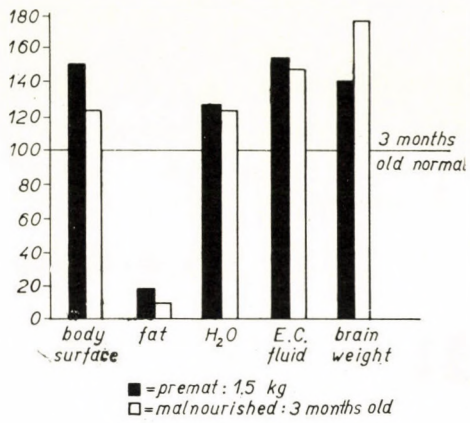

FIG. 2

group presented in Fig. 1 received the same antibiotic and parenteral fluid treatment. The ultimate causes of the high mortality rate in both premature and malnourished infants are under investigation.

BODY COMPOSITION

One of the most striking similarities between prematurity and malnutrition is revealed when studying body composition.

We chose the 3 months old infant as a basis of comparison because at this age some basic physiological constants, thus O_2 consumption and cardiac output, have already reached adult values per unit of body surface.

When compared on this basis, both prematures and marasmics have an increased surface area per unit of weight, their subcutaneous fat is practically non-existent, and their water content, owing especially to the expanded extracellular body fluid volume, is high [6, 8, 11]. Intracellular fluid, when calculated as a percentage of total body water, is low in both groups of infants, 37 per cent, as against 50 per cent in normals. Finally, the brain amounts to a considerable percentage of the body composition.

The curious fact that the brain goes on growing and developing for a time in the malnourished infant, may cause some physiological peculiarities.

THERMOREGULATION

Large body surface area and the lack of insulating subcutaneous fat may have a bearing in both types of infants on one of the weak points of their stability, thermoregulation.

Fig. 3 presents the speed at which hypothermia is arising at environmental temperatures where the 3 months old normal infant is perfectly capable of preserving normal body temperature.

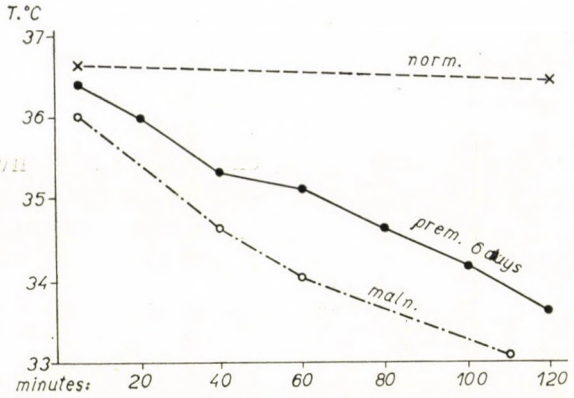

FIG. 3

As to *heat production,* both the malnourished and the young and small premature infants are consuming less O_2 per unit of surface area than the adult or the 3 months old infant. Heat production was measured at environmental temperatures of 20°—25 °C, with the infants kept comfortably warm in swaddling clothes.

In a *cool environment* the rise in O_2 consumption is rather limited in both groups. In lightly clothed (diapers and shirt) prematures put in an environmental temperature of 20 °C, this rise is so small that on a surface basis it hardly reaches the basal level of adults. Adults, when cooled, are capable of producing four to five times as much heat per unit of surface area as the premature.

In malnourished infants we first studied the problem of "chemical regulation" only with reference to low rectal temperatures arising spontaneously. We described in an earlier paper [9] that, in contrast to the cooled hypothermic adult, O_2 consumption does not rise in the hypothermic malnourished infant.

In Fig. 6 we *compare the effects of cooling in the two categories of infants.* The infants dressed only in a short

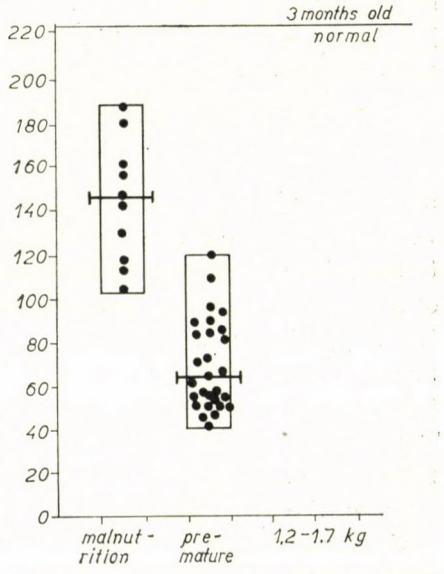

FIG. 4. O_2-consumption measured with diapherometry; rectal temperatures were not below 36°C in this series of measurements. Values measured during periods of restlessness were discarded

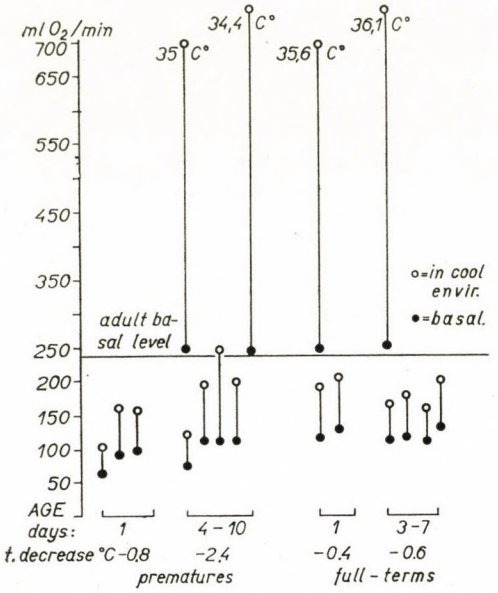

FIG. 5. Lower part: Rise in O_2-consumption in newborn premature and full-term infants in a cool environment (20°C) from basal (•) to maximal level (o). T. Decrease = decrease in rectal temperature at time of maximal rise in O_2-consumption. Horizontal line = adult basal level. Upper part: rise in O_2-consumption and rectal temperatures of cooled adults as drawn from data of DILL and FORBES [4]

shirt were placed in an airtight metabolic chamber of an environmental temperature of 20 °C. Consumption of O_2 was measured continuously with the Kipp-Noyons diapherometer and body temperature by means of a thermocouple inserted in the rectum. The activity of the infants was carefully observed through a glass window in the chamber.

O_2 consumption rose some 40 per cent in the one day old premature infant (weight, 1890 g), while in the severely malnourished 4 months old infant (weight, 2700 g) no rise was observed. The rise in O_2 consumption in the premature seemed to be connected with muscular activity, which was practically absent during the exposure to cool environmental temperature in the malnourished infant.

Within 60 minutes, rectal temperature decreased in the premature by 1 °C, in the malnourished infant by 2° C. — Thus, "chemical regulation" although limited in the premature, was practically absent in the extremely malnourished older infant.

Hypothermia, due to inefficient physical and chemical thermoregulation, may thus easily arise in severely malnourished infants and rectal temperature may drop spontaneously to 25° C. In earlier years this might probably have been one of the ultimate causes of death. According to KULIN's [10] suggestion, such infants should preferably be treated in conditioned wards at environmental temperatures of 25 to 30 °C.

HYPOGLYCAEMIA

One of the major dangers in severe malnutrition is the tendency to spontaneous hypoglycaemia. It arises suddenly, without convulsions, with pallor, coma, a slow-down of the respiratory rate followed by bradycardia. When left untreated, gasping respiration sets in which leads to respiratory paralysis, while the heart continues beating at a slow rate for some minutes [6, 7, 9].

The accidents described are certainly due to hypoglycaemia, as shown in Fig. 7 and Fig. 8.

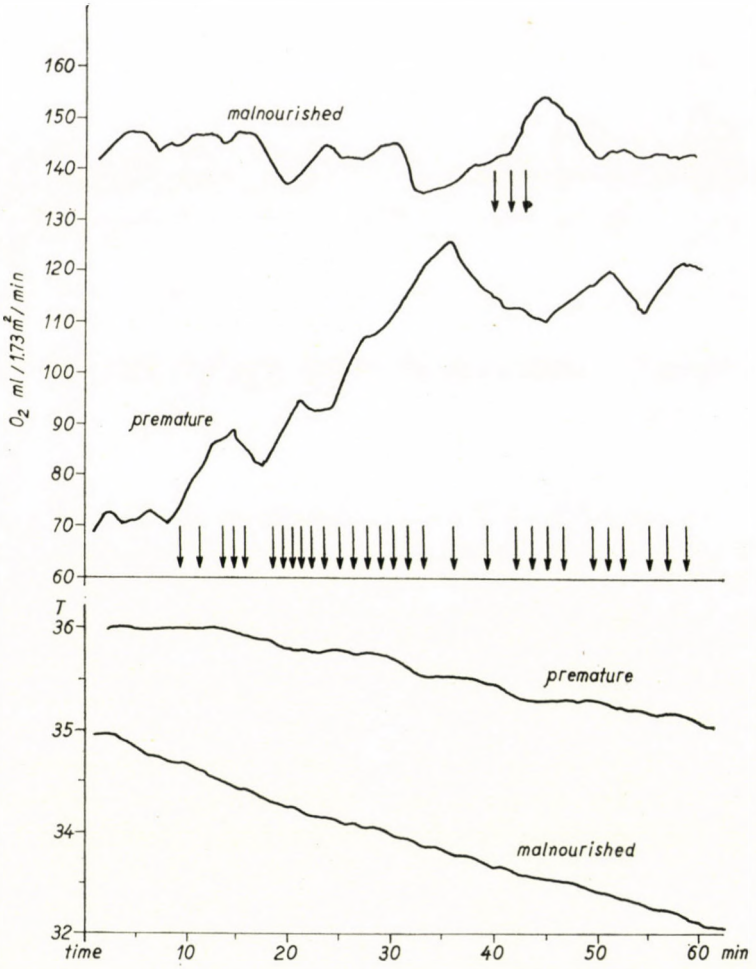

FIG. 6. Premature infant. Age 1 day; weight 1890 g. Abscissa: time in minutes. Upper part of figure: O_2-consumption, ml/1.73 m^2 body surface. Arrows represent muscular activity. Lower part of figure: rectal temperatures, in centigrades

Fig. 7 shows that cerebral arterio-venous O_2 difference, while unchanged at a blood glucose level of 36 mg/100 ml, suddenly decreases when blood sugar falls to 25 mg/100 ml. This decrease in arterio-venous O_2 difference indicates a decrease in O_2 consumption of the brain due to lack of substrate. Following a hypertonic glucose injection, with the rise of the blood sugar level the arterio-venous O_2 difference expands, indicating an increase in cerebral O_2 consumption.

Another proof of the hypoglycaemic origin of the clinical picture described is the dramatic effect of glucose in-

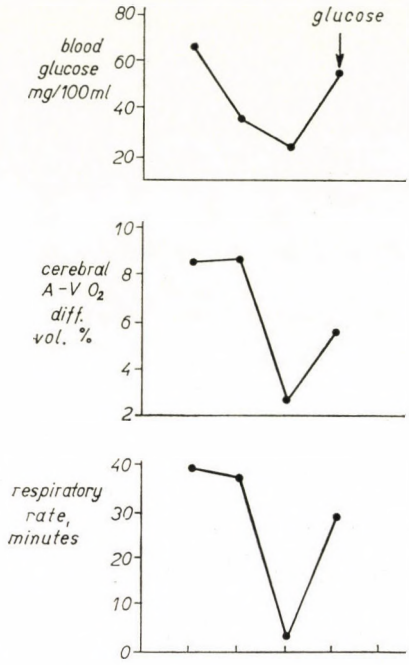

FIG. 7. Observations in hypoglycaemia due to fasting in a severely malnourished infant. Venous O_2 content was measured in the longitudinal sinus, arterial O_2 content in a temporal artery, according to van Slyke. Glucose was measured according to Hagedorn and Jensen

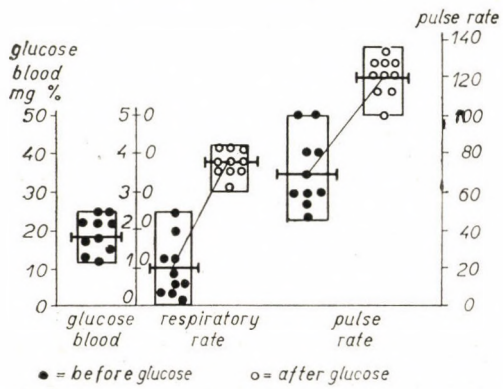

FIG. 8. Left part of figure: glucose levels in blood (Hagedorn and Jensen) at the time of accidents. Right part: change in respiratory and pulse rate following intravenous injection of glucose solution. The horizontal lines in each figure indicate mean values calculated from individual observations (dots)

jection; following this the respiratory and pulse rates rise to normal in some minutes.

These observations, revealing a fatal lack of stability in the blood sugar regulation of malnourished infants, invite to draw a parallel between blood sugar regulation and the possibility of hypoglycaemic accidents in prematures.

In has been known for many years that blood glucose values in the newborn and the premature show a remarkable scatter, with some strikingly low values. The clinical significance of hypoglycaemia, however, has remained unsettled. The conspicuous lack of symptoms at glucose levels known to evoke the clinical syndrome of hypoglycaemia in the adult led to the belief of an increased resistance to hypoglycaemia in the newborn.

In Fig. 9 we have compared glucose levels found in different groups of newborns with those found in spontaneous hypoglycaemia provoking accidents in the malnourished infants.

We are fully aware of the fact that the comparison of blood sugar values in the groups presented is open to some criticism, because of the different methods used.

According to HALLMAN [3], "true sugar" values should be some 20 mg/100 ml lower than values obtained by the Hagedorn-Jensen method. The latter was used in most prematures as well as in the malnourished infants. Thus the "range of accidents" in the malnourished group ought to be at lower sugar values with the use of the Somogyi-Nelson method.

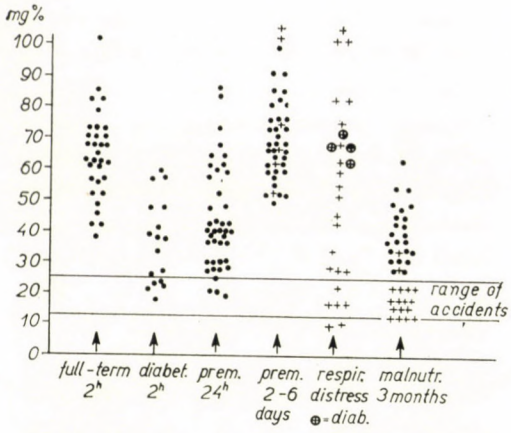

FIG. 9. Data for normal full-term newborn babies (column 1) and newborn babies of diabetic mothers (column 2), drawn from data of FARQUHAR [2]; method: RAMSAY's. Column 3 from data of PINCUS et al. [15]; method: FOLIN and WU's. Columns 4 and 6 give our own observations of 2 to 6 day-old prematures after 6 hours of fasting (crosses indicate values before death), and of malnourished infants. Crosses in column 6 indicate severe accidents, the dots six hours' fasting; method: Hagedorn and Jensen's. Column 5: preterminal values in distressed babies. Drawn from data of NORVAL [14], FARQUHAR [2], WARD [16], and our own observations

The first question is whether there are newborn infants whose blood sugar may fall spontaneously to levels comparable to those invariably causing accidents in malnourished infants. The second question is whether such low values would be accompanied by alarming symptoms. In other words, is the newborn more resistant to hypoglycaemia than the older infant?

The figures for newborns and prematures have been taken partly from the literature and partly from our own observations. From the first column of Fig. 8 containing blood sugar values observed by FARQUHAR [2] in full-term infants two hours after birth, it can be seen that even though some values are low, none of them approaches the "danger zone" found in hypoglycaemic malnourished infants. In newborns of diabetic mothers some lower figures can be noticed, falling in our "zone of accidents". Clinical signs, however, are absent. The same holds true for prematures observed during the first day of life. Between the second and sixth days after feeding has begun, no figure approached the "zone of accidents." In column 5 preterminal figures found by different authors as well as by us in respiratory distress syndrome were pooled. There is a wide scatter with some figures falling in the "danger zone."

The evidence suggests that although low blood sugar figures are frequent in the newborn and the premature, dangerously low levels, however, are rather exceptional and not to be expected in the healthy newborn infant or the premature after feeding has begun. Diagnostic problems with respect to hypoglycaemia may occasionally arise in three categories of infants, viz. in some newborns of diabetic mothers during the first hours, in prematures during the first day of life, and, finally, in some distressed babies. Most of the low figures found in these categories of the newborn, however, were either unaccompanied by symptoms, or, as in the respiratory distress syndrome, there were other pathologic changes that could be held responsible for the ob-

served difficulties. Resistance to hypoglycaemia, owing probably to lower differentiation of the brain, as reflected by its lower metabolic needs, seems to be greater than in the older malnourished infant. On the other hand, whatever the difference in resistance, it cannot be unlimited. As seen in Fig. 7, the arterio-venous O_2 difference remaining normal at a glucose level of 36 mg/100 ml decreased suddenly when blood glucose

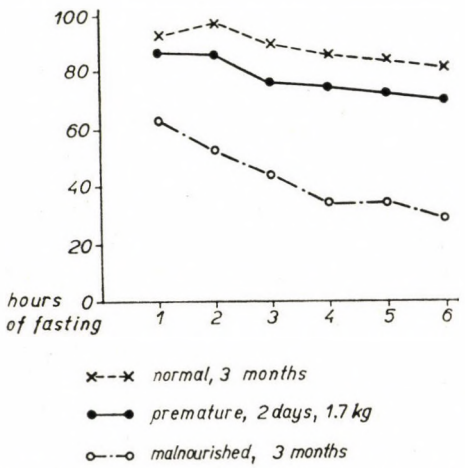

FIG. 10. Method: Hagedorn and Jensen's

was further reduced by only a few mg/100 ml. Thus, at low glucose levels even small changes may provoke accidents. In the last three groups of infants occasional glucose values were so low indeed, that in case of symptoms similar to those described in malnutrition the causal role of hypoglycaemia should be taken into consideration.

On the whole, the regulation of blood sugar in the normal as well as in the premature infant is more stable than in the malnourished infant.

In Fig. 10 the average figures of 6 normal infants 3 months of age have been compared to those of 6 malnourished infants and of 6 two days old prematures, respectively. For 6 hours blood sugar (Hagedorn-Jensen) was measured every hour after the last meal. It may be seen that while the glucose level decreased to very low values in the malnourished infants within 2 to 3 hours after the last meal, values in the prematures remained closer to the normal than to those of the malnourished infants.

HORMONAL ASPECTS

Deficient blood glucose regulation in semistarvation is probably one of the many aspects of gradual exhaustion of pituitary control. The observation that hypoglycaemic cases show a stabilization of the blood glucose level following the injection of ACTH or of suspensions of calf pituitary gland, speaks for the above-mentioned possibility [7, 9].

In chronic starvation, and also in infantile marasmus, the pituitary gland, as well as all the glands under pituitary control, lose weight. MULINOS and POMERANTZ [13] found in rats that the gonads and adrenals that had decreased in size under semistarvation, increased in size following the injection of a suspension of pituitary glands of well-fed rats, even though starvation was continued. Accordingly, they describe the hypophyseal function in semistarvation as a condition of "pseudo-hypophysectomy".

In infantile marasmus we found many hormonal functions of the hypophysis to be reduced. The beneficial influence of ACTH or calf hypophysis injection on hypoglycaemia may probably be interpreted as an indirect evidence of a lack of corticotrophin; Drs. MESS and VARGA at our Department found by biological assay that thyreotrophin disappeared from the gland of severely malnourished infants [12], and we found, further, that the eosinophils making up usually 30 per cent of the cell count, disappeared entirely from the hypophysis [5]. According to current knowledge, this is suspected to be the sign of a lack of growth hormone. I may add the observation of HOTTINGER [4] that adolescents who had been starved for years in concentration camps stayed infantile, and that puberty set in only subsequent to realimentation. Some features of instability in infantile malnutrition may thus be hypophyseal in origin and a parallel could be drawn with SHEEHAN's disease or SIMMONDS cachexia of the adult.

Hypophyseal hormones in malnutrition and prematurity

	Malnutrition	*Prematurity*
Thyreotrophin	decreased	present, probably low
Gonadotrophin	decreased	—
ACTH	decreased	?
Eosinophile cells	disappear	present

Less is known about pituitary function in the newborn and the premature. Eosinophile cells were found to be present already in foetal life. According to work in progress at our Department (MESS and VARGA), thyreotrophin is present in both the newborn and the premature. As to the quantitative aspects of this problem, no conclusion can be drawn as yet. Blood sugar regulation, as mentioned above, apart from the first day in prematures, is far from being so unsatisfactory as to suggest a serious deficiency in corticotrophin.

SUMMARY

The loss or decrease of somatic stability occurring in semistarvation shows some similar features to the underdeveloped stability inherent in prematurity.

Analogies have been found in some immunological aspects involving a high mortality rate from infectious diseases; in alterations in body composition; and in limitations of heat conservation and production in cool environment, leading in both conditions to inefficient thermoregulation. The regulation of blood sugar, however, is more stable in prematures, hypoglycaemic accidents being exceptional, while they are the major cause of death in severest malnutrition. Decreased production of hypophyseal hormones certainly plays an important role in some peculiarities of the malnourished infant's physiology. In prematures, however, this aspect of stability has further to be investigated.

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