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Early Malnutrition and Brain Development

By

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Studies with neurophysiological techniques have shown that severely malnourished children with the clinical picture of kwashiorkor or marasmic kwashiorkor, exhibit in the acute stage of the disease distinct deviations from normal. This is true for echoencephalography, transillumination, and motor nerve conduction velocity. Without exception, however, these deviations have proved rapidly and fully reversible.

There is, however, a possibility that such finer functions, as have to be mobilized in intelligence and behavioural tests of different kinds, may have been permanently and irreversibly harmed as a consequence of serious nutritional disturbances in early life.

Traditionally, the brain has been held to be very resistant to undernutrition, even if this is severe in character. As an example may be mentioned studies on pigs, in which severe undernutrition has been found to prevent the body weight from increasing above 3.5% of the normal at 1 year of age, whereas the brain weight increased to 66% of the normal [3]. However, there is after all a reduction of the weight of the brain and the undernourished animals also show various signs indicating disturbances of the central nervous functions.

Another observation which has given a new dimension to the discussions on the effect of early malnutrition on the body in general and on the brain in particular, is the recognition that there are vulnerable periods in the development of the organs of the body, including the brain, when the effects of malnutrition are not only especially intense but also tend to be irreversible. A well-known example of this observation is provided in the rat experiments of MCCANCE and WIDDOWSON [12] (Fig. 1).

Clinical findings rarely lend themselves to such easy interpretation. However, a number of observations starting with the well-known study by GREULICH [8] in the mid 1950's on Japanese children reared in California and the investigation by MELLBIN on Lappish children in Northern Sweden a few years later [13], lend support to the assumption that an unfavourable early environment, poor nutrition included, will cause permanent stunting of body growth. As more recent evidence for this supposition a diagram from studies per-

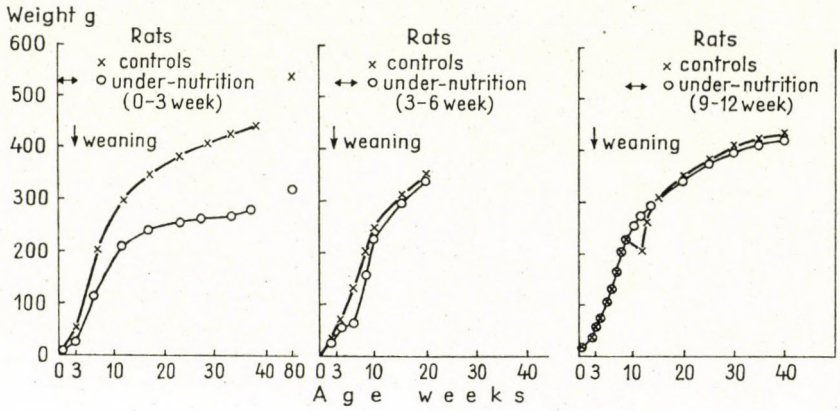

FIG. 1. Bearing of early malnutrition on later development [12]

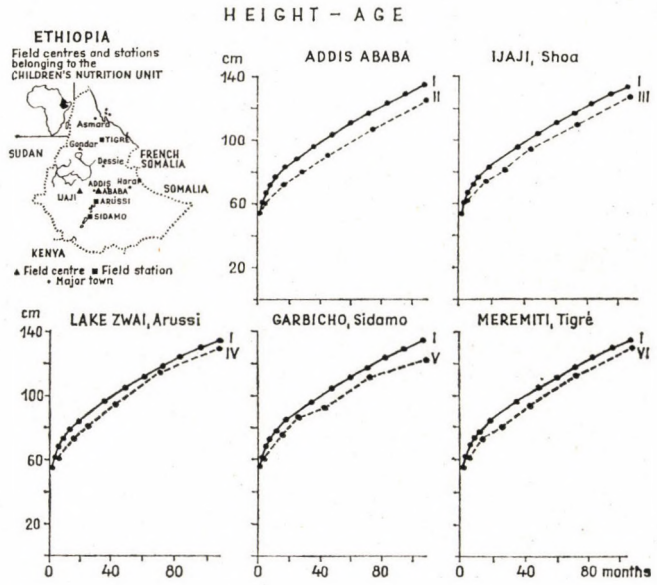

FIG. 2. Height for age in 5 groups of Ethiopian non-privileged children [20]

formed by our own group in Ethiopia [20] (Fig. 2) is presented.

It may be asked how we know that the difference observed is environmental and not genetic in origin. The answer is that, in our studies as in a number of others from various parts of the world, it has been demonstrated that children belonging to the same ethnic groups with parents who are well off and well educated manifest growth and development patterns which come pretty close to European and US standards.

Why is it that early unfavourable influence has permanent sequelae

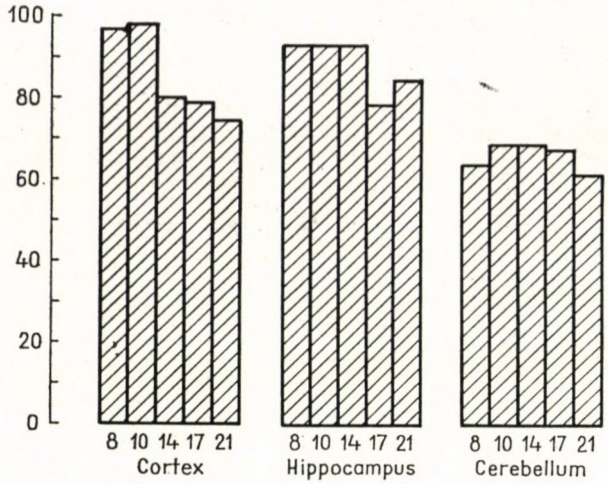

FIG. 3. Effect of malnutrition on the DNA content of different parts of the rat brain [22]

for growth and development, whereas later in life such effects are only transitory? The answer came in the mid 1960's and is now well-known. Any harmful influence which hinders cell multiplication in a given organ so that the total number of cells, as revealed by DNA analysis, is below par when the period of cell multiplication normally should be at an end, will automatically give a lasting effect on the organ size [cf. 22].

Undernutrition later in life influences only the size of the cells but not their numbers and the former process is a reversible one.

After this general introduction I shall now focus entirely on the problem of early malnutrition and brain development. I shall divide this paper into two parts. The first is a survey of highlights from studies by other workers in different parts of the world. The second gives results obtained by our own group.

I. HIGHLIGHTS FROM OTHER STUDIES

Animal experiments. Much of the work on early malnutrition and brain development has been performed on rats. I shall present only one figure indicating the effect of early malnutrition on this species with respect to DNA content of the brain [22] (Fig. 3).

More recently, DOBBING and SANDS [4] have concluded from their studies on rats that "— the brain has a once and only opportunity to grow correctly which cannot be recovered subsequently."

Now, the pattern of growth and development, and the stage of maturity at birth, etc., are very different in the rat as compared with man, and extrapolation of findings must therefore be made with utmost caution.

As always, experiments on subhuman primates should carry our knowledge an important step further. I shall quote here from two such

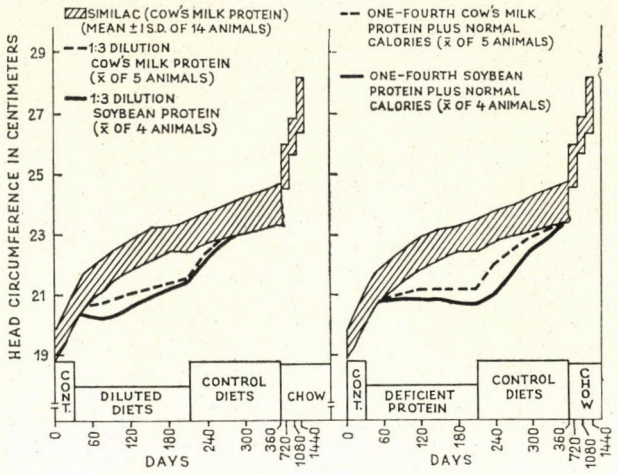

FIG. 4. Head circumference in malnourished infant Rhesus monkeys [21]

studies, one bearing on experimentally induced intrauterine growth retardation, the other on postnatal growth retardation induced by undernutrition or malnutrition.

CHEEK et al. [10], using Rhesus monkeys, ligated the interplacental blood vessel supplying the secondary placental disk after 2/3 of the gestation time (160 days in all). In seven monkeys with birth weights below −2 SD they found a DNA content of the brain which was significantly reduced in the cerebellum, but not so in the cerebrum. It should be noted that the brain of the Rhesus monkey at birth has attained 2/3 of its final weight, as compared with only 1/3 in man.

WAISMAN and KERR [21] induced undernutrition or protein malnutrition in infant Rhesus monkeys between 30 and 210 days of age. Among the preliminary results so far available I shall select only one pertinent to the effect of malnutrition on head circumference (Fig. 4).

Observations in human beings. In children who die with a picture of severe protein-calorie malnutrition the brain weight is reduced in relation to the normal but less so than other organs and the body weight in general. In this respect early findings of KERPEL-FRONIUS and FRANK [11] are well corroborated by more recent studies from developing countries. I take as an example that of BROWN from Uganda [2]. In children who had died with a picture of severe malnutrition he found the weight of the brain to be reduced as follows:

0—1 year	547 grams
1—2 years	800* grams
2—3 years	888* grams
3—4 years	961* grams

* means significant difference from normal

Among the survivors after severe malnutrition, nutrition rehabilitation may create a surprisingly fast catch-up in growth of the brain in so far as head circumference may be used as an indicator. However, as first emphasized by STOCH and SMYTHE in S. Africa [18] this catch-up is not complete, since the head circumference still remains below standard after many years.

It has been claimed that in infants with marasmus the brain size is reduced to an even greater extent than is evident from the head circumference reduction alone, the subarachnoid fluid space being simultaneously abnormally enlarged. As we shall see later on, however, this claim is one of several in the field in question which warrant close scrutiny before being generally accepted.

With respect to the finer structure of the brain in severe malnutrition, special interest is attached to the total number of cells as indicated by DNA analysis. So far, only one study of this kind has been published by WINICK and ROSSO [23] (Fig. 5). Their observations fit well with those made earlier in animals. However, the number of brains examined is limited and the DNA values for normal children given in the figure have been criticized [10]. Thus more studies of this kind are needed before a conclusive standpoint can be reached.

Macro- and microanatomy are interesting enough, biochemistry and function even more so. More than many other organs the brain undergoes fast and fundamental changes in biochemical composition during prenatal and early postnatal life, especially in the first two years. One of the more striking features of this whole maturation process is

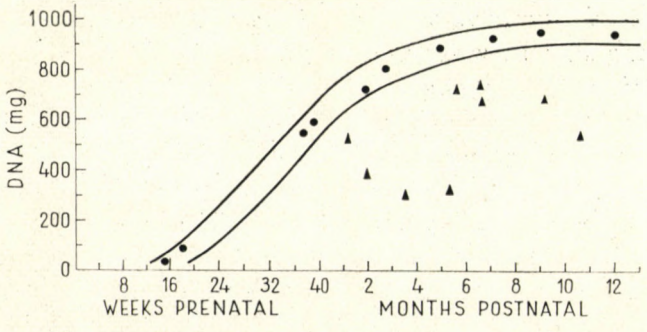

FIG. 5. Reduction in cell number in 9 children who died of malnutrition in Santiago, Chile [23]

the myelinization of the axons. Our knowledge is still incomplete in this field, both with respect to normal conditions and to abnormal development due to malnutrition. However, evidence is accumulating that malnutrition, especially when acting in the most vulnerable period of rapid myelinization, will exert an effect which goes far beyond the period of ongoing, severe malnutrition.

Function. It is a truism to say that the most important with a person is not whether he is big or small, but how he functions. The same is true for the brain of an individual; deviations in size, and even in structure and in chemical composition, from the normal do not in themselves necessarily mean dysfunction (although may often be the borderline to dysfunction). It is necessary, therefore, to analyse function as such. For human beings this means systematic studies of intellectual, emotional and social behaviour of previously malnourished subjects.

Simple as this may sound, in practice it means a formidable task. There is a long shot between measuring after-effects of standardized periods of malnutrition in young rats of an inbred strain, and corresponding studies in human beings under real life conditions. Early malnutrition primarily due to dietary deficiency is today an exceptional event in industrialized countries. Research in this field, therefore, has to be carried out in developing countries. But there again, dietary deficiency is nearly always combined with other deficiencies of the echo system—primitive living conditions, multiple infections, understimulation and/or maternal deprivation. Special measures must be taken to isolate the significance of malnutrition *per se* in this host of unfavourable factors pertinent to the echo system as a whole. An ideal approach should be the study of monovular twins, of whom one has been severely malnourished and the other not, both living in the same environment. But this is a rare achievement. The next best approach, and that mostly used today, is the comparison of siblings belonging to the same family, where one of the siblings has been treated for severe malnutrition and the other not, but otherwise both having been raised under the same environmental conditions. Also in this case there are many snags in the interpretation of the results.

Early studies often failed to recognize all these difficulties and the results do not withstand criticism. Also, they were often cross-sectional rather than longitudinal in character. Today, however, a number of research groups, at least in the order of a dozen, from Guatemala and Chile in the West to India in the East, are engaged in systematic studies on the after-effects of early malnutrition on mental function, involving teams of specialists and carefully standardized testing procedures.

I should like to quote here some recent experiences from two of these groups.

YAKTIN et al. from Beiruth [24] compared three groups: controls, mal-

nourished children who were stimulated, and malnourished children who were not given any extra stimulation during their hospital stay. The Development Quotients (DQ) at the start were 106, 52 and 49, respectively, and after 4 months of nutrition rehabilitation, 79 and 69 for the second and third group. Continued testing after discharge from hospital showed an equalization of the two previously malnourished groups of DQ around 85 as compared with around 105 in the controls. An analysis of the material with respect to age at admission indicated that the catch-up in DQ was the poorer the older the child — and probably the longer the duration of malnutrition when the child was first seen.

BIRCH et al. compared 37 children who had been hospitalized for kwashiorkor in the age period 6—30 months, — the majority being 5—7-years-old at follow-up — with sibling controls who were all within 3 years of the index cases but had never experienced a bout of severe malnutrition. The test used was the Wechsler Intelligence Scale for Children, using both full scale, verbal and performance IQ. The full scale IQ of the index cases was 68.5 and of the controls 81.5. Verbal and performance differences were of similar magnitude and in the same direction. It should be noted that, not unexpectedly, the sibling controls were also considerably below normal.

II. RESULTS OBTAINED BY OUR GROUP

Our studies have been carried out in Ethiopia, using the resources of the Ethiopian Nutrition Institute. This institute has been built up with Swedish support during the last decade, and is a combined research and public health establishment. Much of the research and development work has been directly related to applied nutrition programs. In addition, however, some more basic problems have been tackled, including the effect of early severe malnutrition on brain development. For various reasons our study has been focussed primarily on variables which could be measured with neuro-physiological techniques — echoencephalography, transillumination and nerve conduction velocity. A special program for the study of psychomotor development has been worked out, but this study has not yet been completed.

Under the conditions prevailing in Ethiopia the clinical material of early, severe malnutrition is abundant. For the classification of PCM we now use the definition quoted by HANSEN [9]:

	60—80% expected weight	<60% expected weight
No oedema	Underweight	Marasmus
Oedema	Kwashiorkor	Marasmic Kwashiorkor

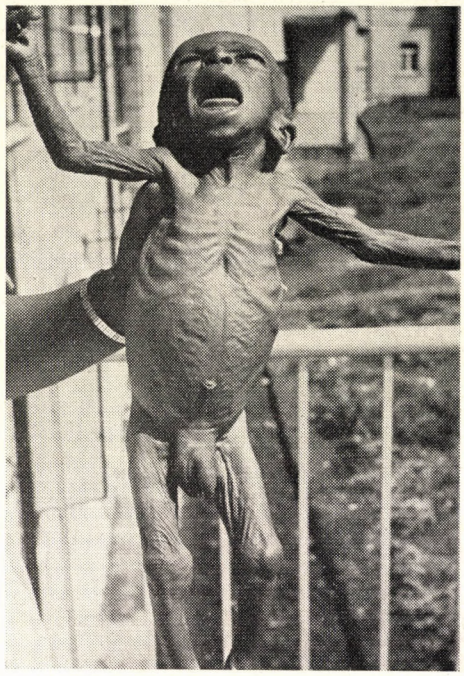

FIG. 6. Ethiopian child with severe protein-calorie malnutrition ("marasmus"). Photo: Y. Hofvander

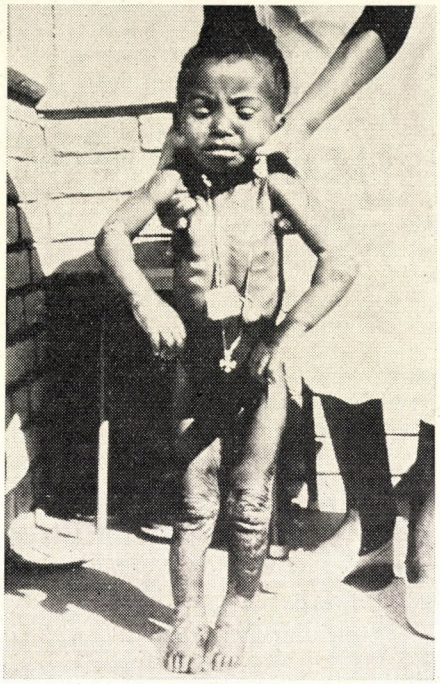

FIG. 7. Ethiopian child with severe protein malnutrition ("kwashiorkor"). Photo: Y. Hofvander

And now to the results of our study. First, two pictures illustrating the type of disease patterns with which we are dealing (Figs 6 and 7).

Echoencephalography

SJÖGREN has proved that during the first few years of life this method can be used for accurate determination of the width of the lateral ventricles [16]. Since the method is completely harmless for the child the examination can be repeated at intervals over a long period of time.

The following figures show data from a study with this technique on Ethiopian children with marasmus and with kwashiorkor (or more accurately, predominantly marasmic kwashiorkor) (Figs 8—12).

Continued studies on a larger material and with longer follow-up times have added further proof that the increase in size of the lateral ventricles in kwashiorkor is a regular phenomenon but also that it is transitory in character. Already 2—3 months after admission when the children were well under way in their nutrition rehabilitation, the indices had returned to normal [5].

For the time being we have no good explanation for the findings. It adds one more dimension, however, to the serious effects of kwashiorkor on the brain of the victims.

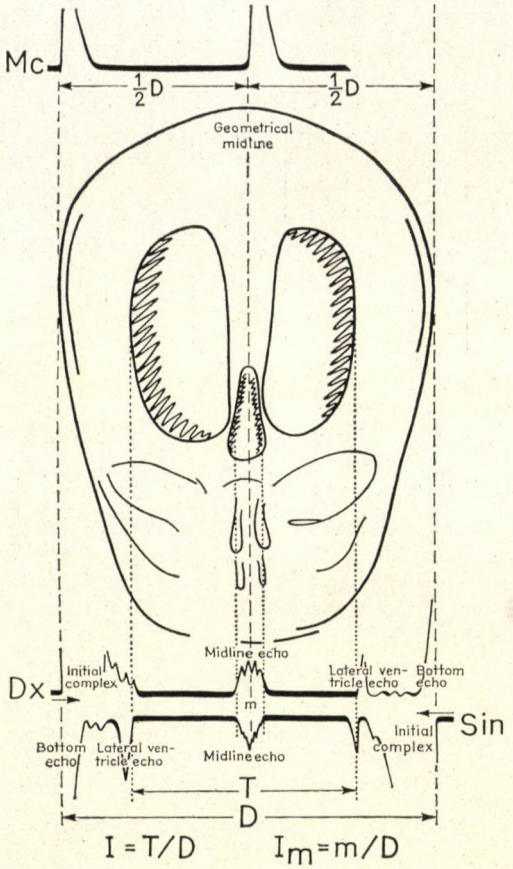

FIG. 8. Schematic pneumogram compared with enlarged schematic echoventriculogram [16]

Transillumination

Transillumination is again a technique which is adaptable and useful primarily in the examination of the young child. It has gained a special reputation in the diagnosis of subdural haematoma. However, as long as the skull bone is thin enough, it will indicate the presence of any kind of increased fluid within the skull, be it a superficial layer exceeding 0.3—0.5 cm in thickness, or a pronounced hydrocephalus internus with a cortical layer less than 1.0—1.5 cm thick.

In a study from Santiago de Chile, ROZOVSKI et al [15] reported transillumination findings which were highly abnormal and, indeed, spectacular, in children below 1 year of age with severe malnutrition. Aspiration of fluid after puncture confirmed that there was an increased

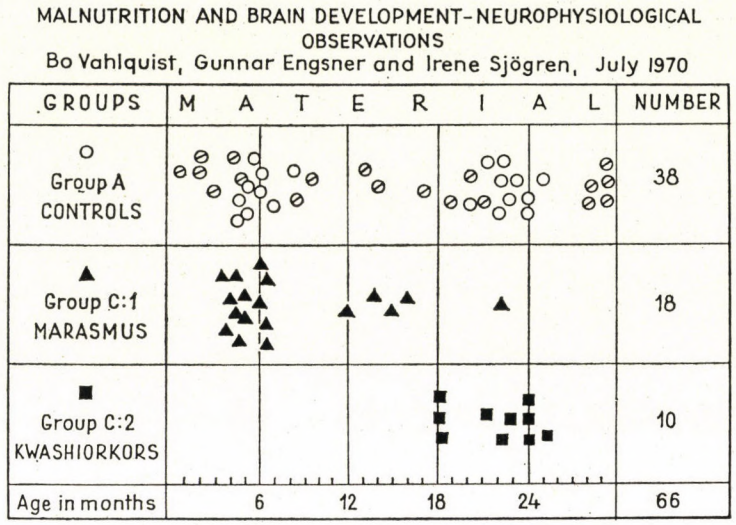

FIG. 9. Age distribution of children studied [19]

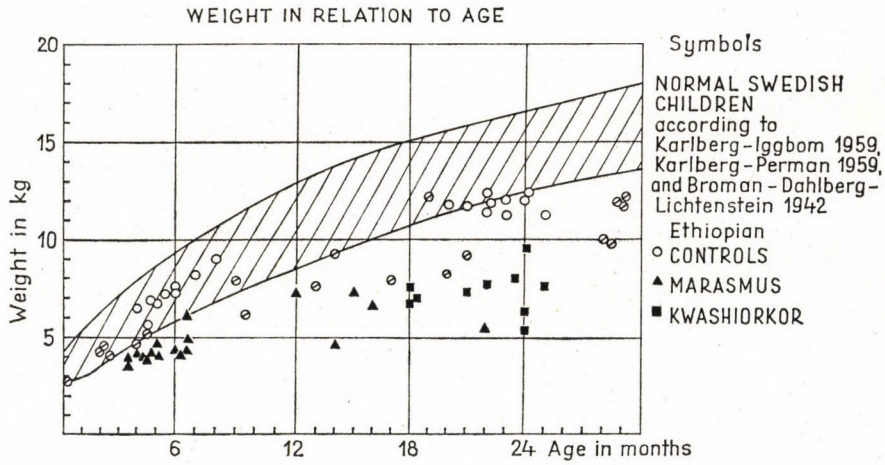

FIG. 10. Weight in relation to age

layer of fluid on the brain surface, probably located to the subarachnoid space. The Chilean scientists comment on "a diminished brain size, creating a space in the interior of the cranium which secondarily fills with cerebrospinal fluid".

Now, can this observation be generalized without reservation to other parts of the world? Seemingly not. ENGSNER et al. [5] carried out transillumination in a large number of Ethiopian children both normal and several malnourished, some 180 in all.

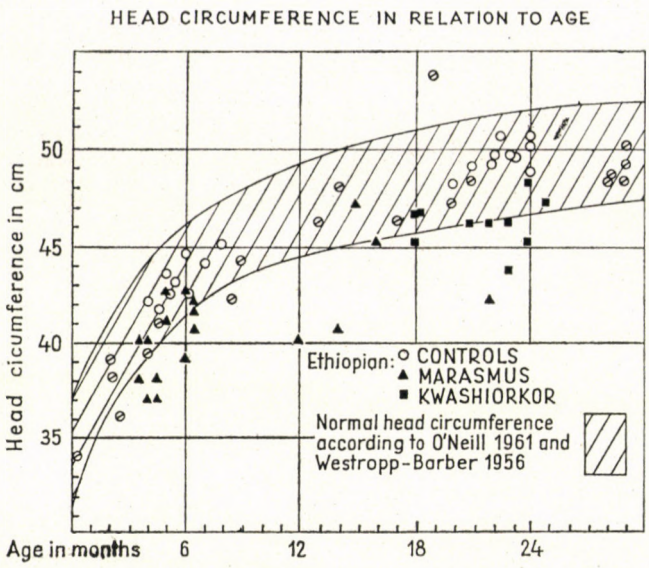

FIG. 11. Head circumference in relation to age [19]

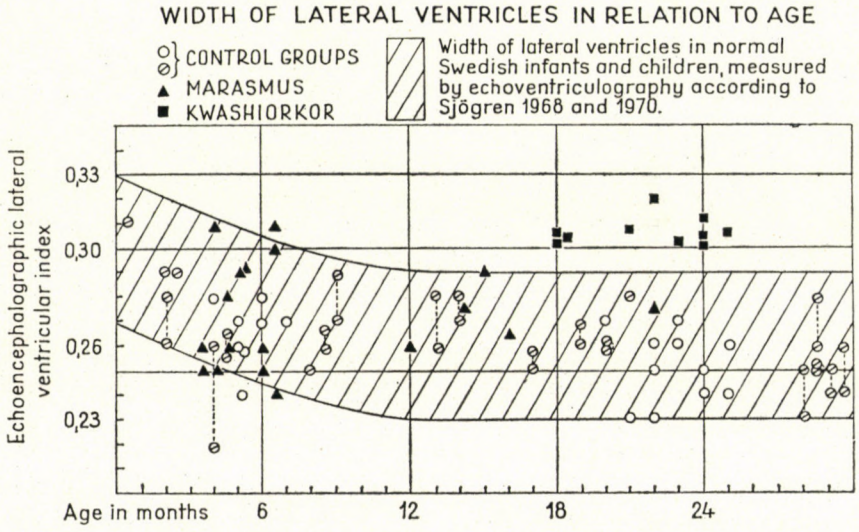

FIG. 12. Width of lateral ventricles in relation to age [19]

The technique used was a semi-quantitative one with registration of the size of the light halo on a calibrated plexi-glass (Fig. 13).

The results can be briefly summarized as follows [6]. Infants with marasmus who had passed 6 months of age showed a very slight increase in

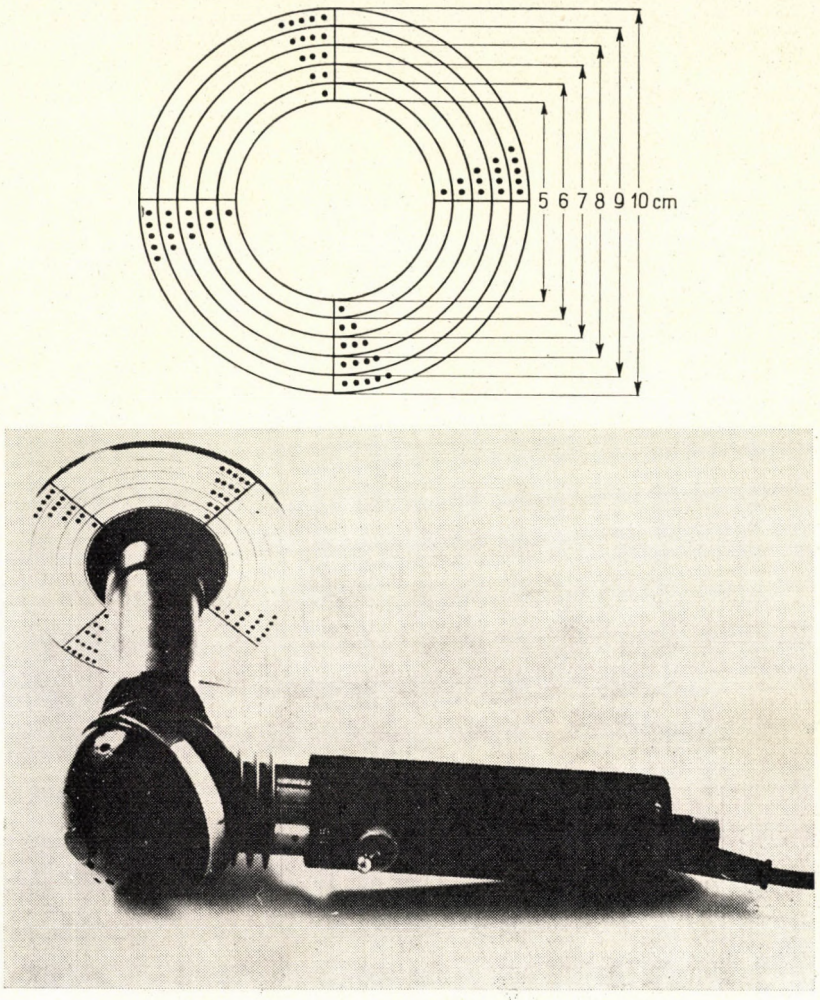

FIG. 13. Transillumination lamp with pointed scale [17]

transillumination which could probably be explained by reduced thickness of the skull bone alone. Below 6 months of age transillumination showed no deviation at all in the children with marasmus. In the kwashiorkor group, with a mean age of about 2 years, the transillumination findings on admission were moderately, but definitely abnormal. This finding could only in part be explained by the thinness of the skull bone and/or oedema of the skin. However, once nutrition rehabilitation had been started, the abnormalities began to decline and vanished completely within the next few months.

It is hard to understand why these great differences exist between the Chilean and Ethiopian children. It is

true that in the Chilean study a much stronger light source was used (800 W), but the light source used in our studies (25 W) should also easily have disclosed any marked fluid accumulation, as has been amply demonstrated by MATTHES and other paediatric neurologists. At the moment I should just like to underline once more what great caution must be observed in generalizing findings from one clinical material to another.

Motor nerve conduction velocity

Here again ENGSNER et al. [7] performed a series of studies on children with marasmus and with kwashiorkor, some 40 in all; and in addition, of course, a normal material. Three nerves were examined routinely, ulnar, median and peroneal.

Children with marasmus, of three different age groups, 0–6, 6–12 and 12–24 months, all showed a moderate but distinct reduction of nerve conduction velocity, most pronounced in the median nerve. During nutrition rehabilitation the abnormality disappeared gradually, usually within 1–3 months.

In 10 children with kwashiorkor, mean age 20 months, the reduction of nerve conduction velocity was considerably more marked, down to 50–60% of the value normal for the age. Roughly one third of this deviation could be explained by peripheral hypothermia. But the remaining two thirds must be interpreted as emanating from true nerve dysfunction. However, here again the findings were transitory in character. Normal values were reached usually within 4–5 weeks after the start of nutrition rehabilitation. In this case the results of the studies fit well with those of a few carried out earlier [14].

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