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# Liver Composition in Kwashiorkor and Marasmus[1]

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## INTRODUCTION

Malnutrition in young children is prevalent in all underdeveloped countries of the world (Scrimshaw and Béhar, 1959; Waterlow *et al.*, 1960). Knowledge of clinical, biochemical, physiological and pathological features of the different syndromes characterizing protein malnutrition has grown rapidly within the last few years (Béhar *et al.*, 1959; Pérez, 1959; Scrimshaw, 1959; Waterlow *et al.*, 1960). However, few comparative studies on the liver composition in the two more common syndromes of malnutrition in children, kwashiorkor and marasmus, are found in the literature (MacDonald, 1959, 1960; Waterlow, 1960; Waterlow *et al.*, 1957).

This paper reports a series of measurements of the gross composition of livers in kwashiorkor and marasmus as they occur in Central America.

## MATERIALS AND METHODS

Children who had died in the Roosevelt Hospital of Guatemala City during the first few days after admission were selected on the basis of their medical and socio-economic history, and physical examination at autopsy, and divided into three groups: "apparently well-nourished," those who had kwashiorkor and those who had marasmus.

In the "apparently well-nourished" group, designated as the control group, eight children were studied. All these children appeared to have been in a good state of nutrition, and had a thick adipose subcutaneous layer at the abdominal wall which averaged 1.2 cm. None presented either edema, or skin and hair lesions. The most frequent terminal causes of death were bronchopneumonia or an upper respiratory infection. Diarrhea of unknown etiology was recorded in three cases. In general, the livers had a normal appearance, but in some cases mild fatty infiltration, believed due to the terminal infection, was observed.

In the kwashiorkor group seven cases were included. All had edema, as well as skin and hair lesions. Their heights and weights were well below the normal. The very small amount of subcutaneous fat of the abdominal wall was found to average 0.2 cm. The main terminal cause of death was diarrhea of unknown etiology, and in some of the cases bronchopneumonia was superimposed. This group was the most difficult to assess due to the varying degrees present in the relative deficiency of protein to total caloric intake. The principal criteria of classification were the

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presence of edema and skin lesions. The livers from this group all looked grossly fatty, although in some fatty change was mild.

Eight children were included in the category of marasmus. All showed marked muscle-wasting and were extremely underweight and small for their ages. None of them presented edema or skin or hair lesions. They had no visible subcutaneous fat. Diarrhea of unknown etiology and acute bacterial enterocolitis were recorded as the main causes of death. All the livers without exception were darker than those of the other two groups, and normal in appearance.

Table I presents the general characteristics of the groups studied. The children in the kwashiorkor group were older than those in either the marasmus or control groups. Because of this discrepancy in ages, it was necessary to compare each group

TABLE I
GENERAL CHARACTERISTICS OF THE GROUPS STUDIED

| | Number of cases | Age (months)[a] | Percentage of Standard: Weight | Length | Liver weight | Liver weight per cm length |
|---|---|---|---|---|---|---|
| | | | Control | | | |
| Mean | 8 | 11.6 | 81.8 | 102.5 | 84.8 | 82.1 |
| S.D. | | (3–38) | 9.2 | 7.2 | 23.2 | 19.0 |
| | | | Kwashiorkor | | | |
| Mean | 7 | 22.6 | 48.2[b] | 87.1[b] | 67.8 | 78.2 |
| S.D. | | (9–36) | 10.1 | 8.0 | 6.8 | 7.9 |
| | | | Marasmus | | | |
| Mean | 8 | 15.1 | 40.3[b] | 85.1[b] | 56.5[c] | 66.5 |
| S.D. | | (4–27) | 11.4 | 11.3 | 16.6 | 18.5 |
| K vs M | | ns | ns | ns | ns | ns |

[a] Age limits given in parentheses.
[b] Significant at the 1% level of probability.
[c] Significant at the 5% level of probability.

with the standard measurements for normal children of the same age. Therefore, body weight and length, liver weight, and liver weight per centimeter of length are expressed as per cent of these standards. The normal heights and weights were obtained from the curves of the Department of Pediatrics of Iowa State University (Jackson and Kelly, 1945) which are adequate for well-nourished Central American children and have been adapted by INCAP, and the body lengths and organ weights from the Tables of Coppoletta and Wolbach (1933). The children in the control group were much heavier and taller than either the ones with kwashiorkor or marasmus; they were, nevertheless, slightly underweight. Their heights, however, were normal for their ages. The kwashiorkor and marasmic children were all small and very markedly underweight, with the weights lower in marasmus than in kwashiorkor. Livers were heavier in the control children than in either of those with kwashiorkor or marasmus, although these differences were not significant due to the great individual variations.

All the livers were analyzed for water, fat, protein, and ash using standard laboratory methods (Assoc. Offic. Agricul. Chem., 1955). Lipid phosphorus and cholesterol were determined by modifications of the Chen *et al.* (1956) and Abell *et al.* (1952) methods, respectively.

## RESULTS

Table II gives the results expressed per 100 gm of fresh tissue. The water content was significantly higher in the marasmus group than in the kwashiorkor or the control groups. The fat content, determined by ether extraction, was much greater in the children with kwashiorkor and control group than in those children with marasmus. Protein was significantly greater in marasmus than in kwashiorkor, but neither was significantly different from that of the control group. The ash content

TABLE II
LIVER COMPOSITION ON FRESH WEIGHT BASIS
(PER 100 GM)

| | Water (gm) | Fat (gm) | Protein (gm) | Ash (gm) | Lipid P (mg) | Cholesterol (mg) |
|---|---|---|---|---|---|---|
| | | | Control | | | |
| Mean | 66.8 | 13.1 | 17.0 | 1.29 | 105 | 397 |
| S.D. | 8.5 | 10.8 | 3.3 | 0.17 | 31 | 91 |
| | | | Kwashiorkor | | | |
| Mean | 63.5 | 19.0 | 15.2 | 1.10 | 68[a] | 257[b] |
| S.D. | 12.6 | 13.7 | 2.0 | 0.16 | 19 | 80 |
| | | | Marasmus | | | |
| Mean | 76.0[b] | 1.9[a] | 18.5 | 1.37 | 71[a] | 280[b] |
| S.D. | 2.1 | 0.6 | 3.0 | 0.14 | 14 | 36 |
| K vs M | *a* | *b* | *a* | *a* | ns | ns |

[a] Significant at the 5% level of probability.
[b] Significant at the 1% level of probability.

TABLE III
LIVER COMPOSITION ON DRY WEIGHT BASIS
(PER 100 GM)

| | Fat (gm) | Protein (gm) | Ash (gm) | Lipid P (mg) | Cholesterol (mg) |
|---|---|---|---|---|---|
| | | | Control | | |
| Mean | 36.1 | 54.2 | 4.1 | 339 | 1222 |
| S.D. | 17.9 | 16.4 | 1.1 | 116 | 273 |
| | | | Kwashiorkor | | |
| Mean | 46.2 | 47.6 | 3.6 | 211[a] | 844 |
| S.D. | 21.2 | 21.1 | 1.7 | 100 | 495 |
| | | | Marasmus | | |
| Mean | 8.2[b] | 76.9[b] | 5.5[b] | 298 | 1177 |
| S.D. | 2.9 | 7.7 | 0.3 | 70 | 190 |
| K vs M | *b* | *b* | *a* | ns | ns |

[a] Significant at the 5% level of probability.
[b] Significant at the 1% level of probability.

was higher in the marasmus than in the kwashiorkor group, but not significantly different from the control. Lipid phosphorus and cholesterol were higher in the control than in either the kwashiorkor or the marasmus groups.

The differences mentioned before are more marked when results are expressed per 100 gm of dry weight tissue, as shown in Table III, particularly for fat, protein, and ash in the marasmic cases. Lipid phosphorus was significantly greater in the control than in the kwashiorkor group. The differences between control and marasmus did not reach statistical significance. The cholesterol content did not show significant differences when expressed on a dry tissue basis.

TABLE IV
LIVER COMPOSITION ON FAT-FREE WEIGHT BASIS
(PER 100 GM)

| | Water (gm) | Protein (gm) | Ash (gm) | Lipid P (mg) | Cholesterol (mg) |
|---|---|---|---|---|---|
| | | Control | | | |
| Mean | 76.9 | 19.5 | 1.5 | 119 | 474 |
| S.D. | 1.9 | 2.5 | 0.2 | 29 | 180 |
| | | Kwashiorkor | | | |
| Mean | 78.0 | 18.9 | 1.3 | 84[a] | 312[a] |
| S.D. | 2.9 | 1.7 | 0.1 | 20 | 54 |
| | | Marasmus | | | |
| Mean | 77.5 | 18.9 | 1.4 | 72[b] | 286[a] |
| S.D. | 2.3 | 3.0 | 0.1 | 14 | 38 |
| K vs M | ns | ns | ns | ns | ns |

[a] Significant at the 5% level of probability.
[b] Significant at the 1% level of probability.

In Table IV, the liver composition is expressed in terms of 100 gm of fat-free tissue. The differences pointed out in the two previous tables were not observed

TABLE V
ABSOLUTE WEIGHT OF LIVER COMPONENTS PER METER OF BODY LENGTH

| | Fat-free liver (gm) | Water (gm) | Fat (gm) | Protein (gm) | Ash (gm) | Lipid P (mg) | Cholesterol (mg) |
|---|---|---|---|---|---|---|---|
| | | | | Control | | | |
| Mean | 270 | 208.7 | 39.0 | 52.4 | 3.95 | 332 | 1210 |
| S.D. | 81 | 65.1 | 28.1 | 15.6 | 0.95 | 131 | 380 |
| | | | | Kwashiorkor | | | |
| Mean | 278 | 217.5 | 67.1 | 52.1 | 3.91 | 227 | 876 |
| S.D. | 52 | 46.0 | 54.3 | 7.5 | 0.55 | 45 | 255 |
| | | | | Marasmus | | | |
| Mean | 268 | 208.8 | 5.5[a] | 50.4 | 3.65 | 189[b] | 777[b] |
| S.D. | 117 | 92.9 | 3.3 | 22.7 | 1.88 | 83 | 372 |
| K vs M | ns | ns | [b] | ns | ns | ns | ns |

[a] Significant at the 1% level of probability.
[b] Significant at the 5% level of probability.

when fat, the main variable, was taken out. Water, protein, and ash content became similar in the three groups. It should be noted that the variances are smaller when the values are expressed in this way. Lipid phosphorus and cholesterol content, when expressed on a fat-free tissue basis, are higher in the control than in the kwashiorkor and marasmus groups.

In order to compare the same groups, in regard to the total components measured, as found in the individual livers, it was necessary to express the results as related to individual body length. The results are shown in Table V. No difference was found in water, protein, ash or total fat-free liver weight among the three groups when compared in this way. Fat was significantly greater, however, in the control and kwashiorkor, than in the marasmus group. Lipid phosphorus and cholesterol content were greater in the control group than in the children with marasmus. The difference between kwashiorkor and marasmus was not significant.

## DISCUSSION

The livers of children with kwashiorkor have been shown to have various degrees of fatty change (Chanda, 1958; Gillman and Gillman, 1945; MacDonald, 1959, 1960; Meneghello *et al.*, 1950; Niemeyer and Meneghello, 1950; Scrimshaw *et al.*, 1958; Sheth and Warerkar, 1959; Sriramachari and Ramalingaswami, 1953; Waterlow, 1954; Waterlow and Weisz, 1956; Waterlow *et al.*, 1957, 1960). In severe cases almost every cell is distended by a large globule of fat giving the liver a honeycomb appearance and showing the nucleus and remaining cytoplasm forced to the periphery of the cells (Scrimshaw *et al.*, 1958; Sriramachari and Ramalingaswami, 1953). The fat appears first in the periphery of the lobule and then spreads throughout the whole liver structure (Scrimshaw *et al.*, 1958). In marasmus, on the other hand, no cells show fatty change and the cytoplasm is more eosinophilic and condensed than in normal hepatic cells. It is obvious from the findings presented in this paper that fatty change of the liver is a characteristic of kwashiorkor and that it is wholly lacking in marasmus.

In spite of the large deposit of liver fat in kwashiorkor, there is no clear evidence of severe liver damage other than the probably mechanical action exerted by the fat. The idea that in tropical areas cirrhosis of the liver in adults is related to fatty livers in early life (Bergouniou and Trémolieres, 1952; Gillman and Gillman, 1945; Trowell *et al.*, 1952) has been rejected (Sheth and Warerkar, 1959; Waterlow, 1954). Fatty change in the liver does not seem to affect the usual liver function tests (Gomez *et al.*, 1950; Niemeyer and Meneghello, 1950; Sheth and Warerkar, 1959; Waterlow, 1956). In some instances of kwashiorkor, the bromosufalein clearance is reduced, but this is thought to be due to an impairment of the hepatic circulation (Waterlow, 1956). The abnormal thymol turbidity, as well as the cephalin-cholesterol flocculation tests occasionally observed among malnourished children are thought to be related to infection and hepatic regeneration (Gomez *et al.*, 1950). Several changes in liver enzyme activity, however, have been reported in malnourished children. In general, the activities of dehydrogenases, transaminases, cytochrome oxidase, cytochrome reductase and glycolic acid oxidases seem to be well preserved (Waterlow, 1950, 1958, 1960). Cholinesterase, xanthine, and D-amino oxidases, on the other hand, are reduced in activity (Burch *et al.*, 1957; Mukherjee and Sarkar, 1958; Waterlow, 1950, 1958, 1960). Liver catalase and alkaline phosphatase are found higher on admission to the hospital than they are after recovery from kwashiorkor (Mukherjee and Sarkar, 1958). Liver succinoxidase activity seems usually to be reduced (Waterlow and Patrick, 1954).

It has been stated (Waterlow, 1954, 1956; Waterlow and Weisz, 1956; Waterlow *et al.*, 1957, 1960) that in protein malnutrition the liver loses a great quantity of protein as shown when the total liver protein in malnourished children is compared to the standard liver protein content derived from normal weights of livers (Coppoletta and Wolbach, 1933) with an average protein content of 17%. If such a comparison is made with the information here presented, values of 85.6 ($s = 30.9$), 60.7 ($s = 10.0$) and 61.2 ($s = 18.8$) per cent for the control, kwashiorkor, and marasmus groups, respectively, are obtained, values quite similar to those reported previously by Waterlow (1956; Waterlow and Weisz, 1956; Waterlow *et al.*, 1957, 1960). Although these differences can be taken as a liver protein lack in malnourished children, as compared to the total liver protein in normal children, the total liver protein content expressed per unit of body length remains unchanged among the different groups.

Another way of expressing liver protein content is on the basis of liver DNA (Thomson *et al.*, 1953; Waterlow *et al.*, 1960). Waterlow (1954; Waterlow and Weisz, 1956; Waterlow *et al.*, 1960) have reported lower concentrations of liver cytoplasmic protein in children with kwashiorkor or marasmus on the basis of DNA but the results must be interpreted with caution. For example, Ely and Ross (1951) and Lecomte and Smul (1954) have found in protein-deficient young rats that the DNA content of the liver nuclei increases. This has been shown by chemical determination in isolated nuclei, as well as by photometric comparison in histological sections. It is suggested that under nutritional deficiency, liver cell nuclei may pass through severe pyknosis (Ely and Ross, 1951); and it has also been reported that in the early stages of pyknosis the DNA increases in the nuclei (Leuchtenberger, 1950). Another explanation given by Thomson *et al.* (1953) is that the liver cells of young growing animals will eventually undergo mitosis; but, before doing so, they will double their content of DNA. In protein-deficient young animals, growth is inhibited and mitosis may also be inhibited even though the premitotic synthesis of DNA takes place. This could result in an apparent increase in the average DNA content per nucleus.

The results presented in this paper indicate that the chief variable influencing the gross composition of liver is fat. The livers in the different clinical conditions studied differ mainly in the amount of fat deposited within their cells, and the other gross cytoplasmic components remain basically unchanged. The data from the absolute weight of liver components per unit of body length also support the same conclusions. In addition, the ratio of water to protein remains around 4, regardless of the way it is expressed. This agrees with the results of Forbes *et al.* (1956) and Bergström *et al.* (1961) for normal livers. In kwashiorkor and marasmus the liver is smaller, a reflection of a retardation of growth as indicated by body length. The result is that when the total components are expressed per unit of body length, all the values, with the exception of fat, become similar. In other words, despite the greater net loss of nitrogen from the body due to the protein breakdown of other tissues, the liver seems to be protected as a special organ having a high protein turnover and a vital need for protein.

Finally, the liver cholesterol and phospholipid content in kwashiorkor and marasmus were lower than in the control group, and there was no relation between them and the total fat content. MacDonald (1959, 1960) reported that in livers from children with kwashiorkor and marasmus there was a lower percentage of non-saponifiable lipids, no increase in phospholipids and an increase in total lipids. The high cholesterol content reported in some cases of kwashiorkor by Ramalingaswami *et al.* (1952) was not observed in the present study.

SUMMARY

Livers taken post-mortem from seven children with kwashiorkor, eight with marasmus and eight "apparently well-nourished" were analyzed for water, fat, protein, lipid phosphorus, cholesterol, and ash content. The final causes of death in most cases were diarrhea of unknown etiology and acute bronchopneumonia. The nutritional status was assessed from clinical history, socio-economic information, and direct examination. Body weight and length, thickness of the abdominal subcutaneous tissue, and weight of the livers were also recorded. The results were expressed on a fresh, dry and fat-free per cent basis. It was found that the chief variable influencing the gross composition of livers in all three types of cases is the amount of fat. The fat-free tissue apparently remains basically unchanged. When the total liver components, taking into account liver weights, are expressed per unit of body length, all the values, with the exception of fat, become similar. The fatty change of the liver is a characteristic feature of kwashiorkor, and it is wholly lacking in marasmus.

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