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LONG CHAIN NON-ESTERIFIED FATTY ACID PATTERN IN PLASMA OF CYSTIC FIBROSIS PATIENTS AND THEIR PARENTS.

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SUMMARY

The absolute and the percentage plasma NEFA pattern of healthy children, Cystic Fibrosis (C.F.) patients and their parents have been determined (table I, III, V) and compared with those of age and sex matched control subjects (table II, IV, V).

There is a striking difference in the percentage plasma NEFA pattern of C.F. patients with pancreatic insufficiency : palmitic, palmitoleic and oleic acid are significantly increased while linoleic, linolenic and stearic acid are decreased (table IV). Four C.F. children without pancreatic involvement have the same abnormal NEFA pattern (fig. 3).

The overlapping areas of the distributions of both palmitoleic and linoleic acid (as shown in fig. 2α and β) are small for healthy and C.F. subjects. About 90 % of the C.F. subjects examined show an abnormal palmitoleic and/or linoleic acid concentration. Tested individually, recognition of this typical C.F. pattern involves a possible error of 15 % (fig. 3).

A correlation exists between the abnormality of the plasma NEFA pattern in C.F. patients and the severity of pulmonary disease.

The percentage plasma NEFA pattern of C.F. parents is modified by an increase of linoleic acid and a decrease of saturated fatty acids (table V, fig. 1α, β). This is possibly due to an higher dietary intake of polyunsaturated fatty acids.

SPECULATION

It has not been convincingly demonstrated yet that the abnormal plasma NEFA pattern in Cystic Fibrosis is entirely due to malabsorption of dietary essential fatty acids. Rather, a primary defect in fatty acid metabolism also remains possible.

INTRODUCTION

Abnormal fatty acid composition of major blood lipid fractions and of various tissues have been reported in Cystic Fibrosis (C.F.) by several investigators (2, 6, 8, 12-15, 17, 24).

The physiological importance of these fatty acid alterations is unknown. It has been suggested that the metabolic defect in C.F. might be in the area of some clinical manifestations of the disease (11, 18, 24).

Hubbard et al. have studied the fatty acid composition of the various plasma lipid fractions from C.F. patients without pancreatic insufficiency and from obligate heterozygotes. They have concluded that the abnormal fatty acid composition is secondary to malabsorption and is not due to a basic defect in fatty acid metabolism (13).

Therapeutic trials of fatty acid supplementation have been carried out, but very confusing results have been reported (3, 4, 9-11, 16, 25). Several investigators have described a reduction in sweat sodium concentration in C.F. children after intravenous and oral fatty acid supplementation (4, 9-11, 25). More recent published data, however, have not supported these previous findings (3, 16). Clearly, further study remains necessary to interrelate all observations.

In our study we have investigated the fatty acid pattern of the plasma long chain non-esterified fatty acid (NEFA) fraction from C.F. subjects with and without pancreatic insufficiency and from obligate heterozygotes. Until now, only a few and relatively incomplete data, concerning this small lipid fraction, have been published for both healthy and C.F. children (6, 13, 14). Only one study gives information about the plasma NEFA fraction in C.F. parents (13).

Recently, the plasma NEFA pattern for a large group of healthy children and young adults has been determined (21). It has been demonstrated that the total NEFA concentration, the absolute and the percentage NEFA pattern of plasma are very dependent on age and sex. Consequently, in this particular study, we compare the results for the plasma NEFA pattern of C.F. patients and their parents with those of age and sex matched controls.

EXPERIMENTAL

SUBJECTS : 48 patients with proved Cystic Fibrosis have been examined in age groups of 8-10 and 15-17 years old. - These age groups were chosen because the reference blood samples of healthy children were obtained as a part of a study concerning the nutritional and cardiovascular state of the young Belgian population. This particular study was performed on subjects of 8-10, 15-15 and 20-25 years old. - Only four out of the 48 subjects had definitely no pancreatic insufficiency as was established by duodenal intubation for enzyme activity, by determination of nitrogen and lipid absorption coefficients (1) or by determination of trypsin activity in stool samples (7). These four children did not suffer from steatorrhoea and did not require pancreatic enzyme preparations.

A description of the large control group of healthy children and details about the conditions of blood sampling are published elsewhere (21).

32 obligate heterozygotes (parents of C.F. patients) have also been studied. The obtained results are compared with those of 28 healthy adults of the same age (35-45 years old) and sex. From all the healthy subjects and from the parents of the C.F. children studied, informed consent was obtained for blood sampling of their children and of themselves.

MATERIALS :

As described previously (19).

METHODS :

As described previously (19, 20).

In short, after blood samples were collected into ice-cooled heparinised tubes (100 I.U./ml blood), the plasma was separated from the red blood cells within a limited time (20). A known concentration of heptadecanoic acid was added as internal standard and the total lipids were extracted twice using a mixture of isopropanol, n-heptane and 1N sulfuric acid (39/8/1/; v/v). The various lipid fractions were separated by one dimensional thin-layer chromatography with n-heptane, diethylether and acetic acid (40/10/1; v/v). The NEFA spots were scraped off and extracted with purified diethylether. After methylation with boron trifluoride in methanol (14 %; w/v), the methyl esters were extracted with n-heptane and separated by gas-liquid chromatography on a 5 % free fatty acid phase column. A digital integrator (Hewlett-Packard 3380A, USA) was used for the calculation of the results. Simultaneously reference and blank determinations were carried out.

RESULTS

The results concerning the absolute and percentage plasma NEFA pattern of healthy children have been described previously (21) and are not resumed here.

- Absolute plasma NEFA pattern

The absolute plasma NEFA pattern and the total NEFA concentration of C.F. children from 8-10 (group I) and 15-17 (group II) years old are shown in table I. For both groups, the absolute concentration of each fatty acid as well as the total NEFA are higher for boys than for girls. Significance is indicated.

For C.F. boys and girls the total NEFA and the individual fatty acid content of plasma significantly decrease from 8-10 to 15-17 years old.

Comparing the total NEFA concentration of C.F. and healthy children, we find that for every age group, the total NEFA concentration of C.F. boys is significantly higher ($P < 0,001$). For girls no significant alterations could be detected. The significant changes between the individual fatty acid concentrations of C.F. and healthy children are mentioned in table II.

For C.F. and healthy parents the mean total NEFA concentration in μM is respectively 435 μM ±191 (N_{CF} =32) and 317 μM ±133 (n_H =28)(Student's t-test, $P < 0,01$) : for males 360 μM ±122 (n_{CF} =15) and 270 μM ±109 (n_H =17)($P < 0,05$) and for females respectively 517 μM ±184 (n_{CF} =17) and 384 μM ±117 (n_H =11) ($P < 0,01$). The total NEFA concentration and the absolute amounts of the individual fatty acids are significantly higher for C.F. parents than for healthy adults.

- Percentage plasma NEFA pattern

The percentage plasma NEFA pattern of C.F. children is shown in table III. The significant changes between C.F. girls and boys of the same age group are indicated.

There is a striking difference in the percentage plasma NEFA pattern of C.F. children, compared with healthy ones (table IV). Palmitic, palmitoleic and oleic acid are significantly increased, while linoleic, linolenic and stearic acid are decreased. Nearly the same abnormalities are found for C.F. girls and boys of both age groups.

The most important differences in the NEFA pattern of C.F. patients are observed in palmitoleic and linoleic acid. The ratio of palmitoleic to linoleic acid is much higher in C.F. patients than in healthy children (fig. 1α).

Comparing the percentage plasma NEFA pattern of C.F. parents with matched controls, we find some significant changes : palmitic and stearic acid are decreased while linoleic and linolenic acid are increased (table V). The ratio palmitoleic to linoleic acid is changed, but oppositely to that of C.F. homozygotes (fig. 1β).

So far comparisons have been made between groups of C.F. and healthy children. It is also worth while to investigate if individual changes in the percentage plasma NEFA pattern of C.F. patients are significant.

Among the various fatty acids, palmitoleic and linoleic acid show the greatest differences in distribution between healthy and C.F. subjects (see fig. 2α and 2β). The overlapping area of both distributions is small. The non or minor overlapping areas can be represented as in fig. 3. A typical C.F. plasma NEFA pattern can be recognized from this graph. The percentages indicated on the graph represent the possible error involved. Testing the individual concentrations of palmitoleic and linoleic acid for each C.F. child examined; 61,4 % of the C.F. patients show a typical C.F. pattern with a possible error of 3,4 % and 88,7 % with a possible error of 15,5 %.

Four C.F. patients, without pancreatic insufficiency, have the same abnormal NEFA pattern as the C.F. patients with pancreatic involvement. Two patients show (fig. 3) a C.F. pattern with a possible error of 2,6 % and two patients with a possible error of respectively 12,5 and 14,5 %.

Noteworthy is that all the C.F. children in the non-definable overlapping area (the shaded area on the graph in fig. 3) are patients with pronounced pancreatic insufficiency and with little or no pulmonary involvement. Moreover the subjects in the 0-3 % area are mostly patients with severe pulmonary involvement. Pulmonary disease was assessed by the occurrence and the severity of bronchorrhea, respiratory infections and abnormalities in chest X-rays.

DISCUSSION

- Absolute plasma NEFA pattern :

In contrast with our findings for healthy children (21) the results for C.F. subjects show that the total NEFA concentration and the individual fatty acid concentrations are higher for boys than for girls.

The relation with age, established for healthy children (21), does still exist for C.F. patients : for both sexes, the absolute amount of each fatty acid and the total NEFA concentration decrease with age (from 8-17 years).

The total NEFA concentration is significantly higher in C.F. boys than in healthy ones. This is consistent with Kuo's suggestion (15), that under normal conditions, depot fat mobilization is going on at an increased rate in C.F. children.

The total NEFA concentration for C.F. patients with pancreatic insufficiency, as reported in the literature (13), is not comparable with our results, because of the heterogeneity of the group they studied : 6 females and 5 males, aged 14-47 years.

In C.F. parents the plasma total NEFA concentration and the invidual amount of each fatty acid are significantly higher than those of healthy adults. This could partly be due to the higher mean age of our C.F. parents group. Our previous work (22) has shown that the total NEFA and the individual fatty acid concentrations increase with age from 25 to 50 years. No significant difference in plasma total NEFA concentration between normal subjects (aged 19-32 years) and obligate heterozygotes (aged 29-42 years) has been reported (13).

- Percentage plasma NEFA pattern :

The abnormalities, observed in the plasma NEFA pattern of C.F. children are in good agreement with the scant data, described in the literature, concerning the plasma NEFA pattern in C.F. patients with pancreatic involvement (6, 13, 14). Kuo and Huang have reported an increased concentration of palmitoleic and a decreased content of stearic and linoleic acid (14). Caren and Corbo could only detect an increased concentration of palmitoleic acid (6) and Hubbard et al. have described a significant elevation of palmitoleic acid and a decrease of linoleic acid for pancreatic C.F. patients (13).

About 90 % of our C.F. patients with pancreatic insufficiency show an abnormal palmitoleic and/or linoleic acid concentration (fig. 3) Tested individually, recognition of this typical C.F. pattern involves a possible error of 15 %.

Four children without pancreatic involvement present the same abnormal plasma NEFA pattern. As we had the possibility of studying only four children, we can only draw preliminary conclusions, but our results differ from data in the literature (12, 13). Hubbard et al. (13) and Galabert et al. (12) have shown that the fatty acid composition of plasma lipid fractions in C.F. patients without pancreatic insufficiency (respectively n = 5 and n = 15) does not differ significantly from that of normal subjects.

These authors could not observe any correlation between the abnormal fatty acid pattern and vitamin-E deficiency, age, sex or severity of the disease for C.F. subjects with pancreatic involvement. However, we have found a certain correlation between severity of pulmonary disease and abnormality of plasma NEFA pattern in C.F. patients. C.F. patients with little or no pulmonary involvement have nearly normal plasma percentage concentrations of palmitoleic and/or linoleic acid. On the other hand, those with severe pulmonary disease show extremely abnormal palmitoleic and linoleic acid concentrations.

The suggestion made by Campbell et al. (5), that deterioration of lung function in C.F. patients might be correlated with abnormal fatty acid composition of blood lipids cannot be excluded. They suggest that oxygen does not simply diffuse across erythrocyte membranes, but that its transport is influenced by the fatty acid composition of the red cell membrane. The results of our previous work support their suggestion as we have shown that the fatty acid composition of the various red cell membrane phospholipids in C.F. patients is altered in the same way as the fatty acid pattern of the NEFA fraction in plasma (23).

The plasma NEFA pattern of C.F. parents is nearly normal, which is in good agreement with data in the literature (13). The percentage concentrations of the polyunsaturated fatty acids (linoleic and linolenic acid) are increased and the saturated fatty acids (palmitic and stearic acid) concomitantly decreased.

Since the parents of all our C.F. children are advised to use polyunsaturated fats in preparing meals for their children, we think that the high percentages of polyunsaturated fatty acids in their plasma NEFA fraction are a reflection of an higher dietary intake of polyunsaturated fatty acids by the whole family.

From our results for C.F. patients with and without pancreatic insufficiency, it appears that an abnormal plasma NEFA pattern can occur in both groups.

Further study remains necessary to show whether C.F. children have a primary abnormality of fatty acid metabolism or whether the observed disturbances in the plasma NEFA pattern are completely secondary to malabsorption of dietary essential fatty acids.

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Table I. ABSOLUTE PLASMA NEFA PATTERN AND TOTAL NEFA CONCENTRATION OF HEALTHY CHILDREN AND C.F. PATIENTS WITH PANCREATIC INSUFFICIENCY.

F.A.	AGE	♀		♂	
		C.F.	H	C.F.	H
$C_{14:0}$	I	15 ± 11 ⊙⊙	16 ± 12	27 ± 13	14 ± 12
	II	11 ± 7	12 ± 9	17 ± 5	9 ± 7
$C_{16:0}$	I	131 ± 70 ⊙	119 ± 68	183 ± 77	109 ± 55
	II	92 ± 31	102 ± 41	118 ± 26	74 ± 37
$C_{16:1}$	I	63 ± 48	26 ± 20	82 ± 45	22 ± 17
	II	31 ± 15	23 ± 14	42 ± 18	16 ± 13
$C_{18:0}$	I	40 ± 15	49 ± 24	56 ± 34	48 ± 21
	II	33 ± 12	42 ± 18	41 ± 6	33 ± 18
$C_{18:1}$	I	214 ± 101 ⊙	191 ± 112	304 ± 136	168 ± 93
	II	123 ± 45 ⊙	159 ± 72	183 ± 46	112 ± 57
$C_{18:2}$	I	50 ± 27 ⊙⊙	77 ± 49	92 ± 41	73 ± 44
	II	31 ± 18	71 ± 34	48 ± 24	53 ± 30
$C_{18:3}$	I	4 ± 4	8 ± 6	5 ± 3	6 ± 5
	II	3 ± 2	6 ± 3	3 ± 3	5 ± 4
TOTAL NEFA	I	523 ± 249 ⊙	499 ± 282	723 ± 311	442 ± 249
	II	327 ± 107 ⊙	424 ± 197	463 ± 109	308 ± 149

Values are presented as mean concentration in µM ± standard deviation.

For group I : 8-10 years old; $n_{CF♀}$ =16 and $n_{CF♂}$=16; $n_{H♀}$ =94 and $n_{H♂}$=103.

For group II : 15-17 years old; $n_{CF♀}$ =6 and $n_{CF♂}$=6; $n_{H♀}$ =61 and $n_{H♂}$=134.

The significant differences between C.F. boys and girls of the same age group are indicated.

Student's t-test with ⊙ $P < 0,05$ and ⊙⊙ $P < 0,01$.

Abbreviations used for fatty acids : $C_{14:0}$ myristic acid; $C_{16:0}$ palmitic acid; $C_{16:1}$ palmitoleic acid; $C_{18:0}$ stearic acid; $C_{18:1}$ oleic acid; $C_{18:2}$ linoleic acid; $C_{18:3}$ linolenic acid.

Table II : SIGNIFICANT CHANGES IN THE ABSOLUTE PLASMA NEFA PATTERN AND THE TOTAL NEFA CONCENTRATION OF C.F. CHILDREN WITH PANCREATIC INSUFFICIENCY, COMPARED WITH HEALTHY ONES.

F.A.	AGE	♀	♂
		SIGNIFICANCE	SIGNIFICANCE
$C_{14:0}$	I		▲
	II		▲
$C_{16:0}$	I		▲
	II		▲
$C_{16:1}$	I	▲	▲
	II		▲
$C_{18:0}$	I		
	II		
$C_{18:1}$	I		▲
	II		▲
$C_{18:2}$	I	△	
	II	▲	
$C_{18:3}$	I	▲	
	II	△	
TOTAL NEFA	I		▲
	II		▲

Abbreviations used for fatty acids are mentioned in the footnote of table I.

▲ increase $P < 0,01$ and △ increase $P < 0,05$.

Student's t-test with n as indicated in table I.

Table III : PERCENTAGE PLASMA NEFA PATTERN OF HEALTHY CHILDREN AND C.F. PATIENTS WITH PANCREATIC INSUFFICIENCY.

F.A.	AGE	♀		♂	
		C.F.	H	C.F.	H
$C_{14:0}$	I	2,6 ± 1,3 ⊙	2,9 ± 1,3	3,6 ± 1,0	3,0 ± 1,3
	II	3,1 ± 1,1	2,8 ± 1,8	3,9 ± 0,8	2,7 ± 1,5
$C_{16:0}$	I	26,7 ± 3,6 ⊙	24,1 ± 2,1	24,4 ± 2,5	25,0 ± 2,8
	II	28,2 ± 1,7 ⊙	25,3 ± 2,5	26,4 ± 0,8	25,5 ± 2,8
$C_{16:1}$	I	11,3 ± 2,6	4,8 ± 1,8	10,4 ± 2,5	4,6 ± 2,1
	II	9,2 ± 1,9	5,4 ± 2,3	9,0 ± 2,0	4,9 ± 2,3
$C_{18:0}$	I	8,7 ± 2,4	10,6 ± 2,4	8,2 ± 1,9	12,2 ± 3,2
	II	10,8 ± 2,2	10,4 ± 2,3	9,5 ± 1,8	11,4 ± 3,0
$C_{18:1}$	I	40,5 ± 3,7	38,9 ± 3,9	40,0 ± 3,3	37,7 ± 4,3
	II	38,2 ± 2,9	37,5 ± 3,5	40,4 ± 3,5	35,8 ± 3,6
$C_{18:2}$	I	9,6 ± 3,3 ⊙⊙	16,9 ± 4,3	12,9 ± 3,7	16,3 ± 4,0
	II	9,5 ± 0,3	17,6 ± 4,3	10,4 ± 3,4	17,2 ± 5,0
$C_{18:3}$	I	0,9 ± 0,9	1,8 ± 1,2	0,6 ± 0,4	1,4 ± 1,0
	II	1,3 ± 0,7	1,3 ± 1,2	0,7 ± 0,7	1,6 ± 1,4

Abbreviations used for fatty acids are mentioned in the footnote of table I.

Values are presented as mean percentage concentration ± standard deviation.

For group I : 8-10 years old; $n_{CF♀}$ =16 and $n_{CF♂}$=16; $n_{H♀}$ =94 and $n_{H♂}$=103.

For group II : 15-17 years old; $n_{CF♀}$ =6 and $n_{CF♂}$=6; $n_{H♀}$ =61 and $n_{H♂}$=134.

The significant differences between C.F. boys and girls of the same age group are indicated.

Student's t-test with ⊙ $P < 0,05$ and ⊙⊙ $P < 0,01$.

Table IV : SIGNIFICANT CHANGES IN THE PERCENTAGE PLASMA NEFA PATTERN OF C.F. CHILDREN WITH PANCREATIC INSUFFICIENCY, COMPARED WITH HEALTHY ONES.

F.A.	AGE	♀	♂
		SIGNIFICANCE	SIGNIFICANCE
$C_{14:0}$	I		△
	II		△
$C_{16:0}$	I	▲	
	II	▲	
$C_{16:1}$	I	▲	▲
	II	▲	▲
$C_{18:0}$	I	▼	▼
	II		
$C_{18:1}$	I	△	△
	II		▲
$C_{18:2}$	I	▼	▼
	II	▼	▼
$C_{18:3}$	I	▼	
	II		

Abbreviations used for fatty acids are mentioned in the footnote of table I.

△ increase $P < 0,05$; ▲ increase $P < 0,01$ and ▼ decrease $P < 0,01$.

Student's t-test with n as indicated in table III.

Table V : PERCENTAGE PLASMA NEFA PATTERN OF HEALTHY AND C.F. PARENTS

F.A.	GROUP	♀		♂	
		mean	S.D.	mean	S.D.
$C_{14:0}$	A	2,1	1,2	2,5	0,8
	B	2,6	0,8	2,2	1,0
$C_{16:0}$	A	27,1	3,2	27,6	2,5
	B	24,3 ⊕	2,9	24,9 ⊕⊕	2,8
$C_{16:1}$	A	4,7	1,5	4,6	1,6
	B	5,9	2,1	4,3	2,4
$C_{18:0}$	A	10,0	2,0	11,5	2,4
	B	8,9 ⊕	1,4	9,8 ⊕	2,3
$C_{18:1}$	A	38,4	3,8	36,6	3,3
	B	37,9	2,2	36,3	3,5
$C_{18:2}$	A	16,7	3,3	15,1	4,9
	B	19,5	4,5	21,5 ⊕⊕	5,7
$C_{18:3}$	A	0,7	0,4	1,2	1,6
	B	1,1 ⊕	0,6	1,2	0,9

Abbreviations used for fatty acids are mentioned in the footnote of table I.
Values are presented as mean percentage concentration and standard deviation.

The significant differences between C.F. parents and healthy adults are indicated.
For group A : healthy adults; $n_{♀}$ =17 and $n_{♂}$=15.

For group B : C.F. parents; $n_{♀}$ =11 and $n_{♂}$=17.
Student's t-test with ⊕ $P < 0,05$ and ⊕⊕ $P < 0,01$.

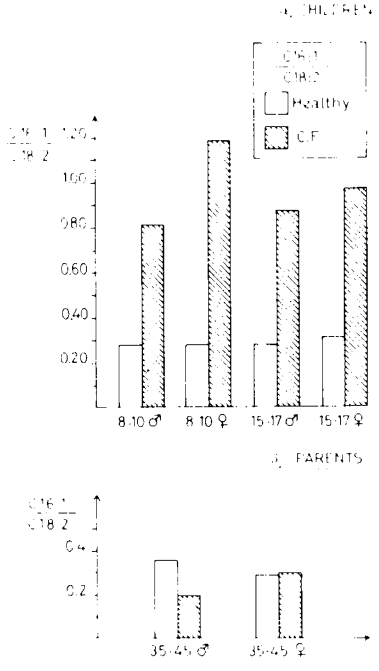


Fig. 1 : Ratio palmitoleic to linoleic acid in the plasma NEFA fraction of healthy and C.F. children (▵) and healthy adults and C.F. parents (▷).

n healthy children = 391 and n healthy adults = 28.

n C.F. children = 44 and n C.F. parents = 32.

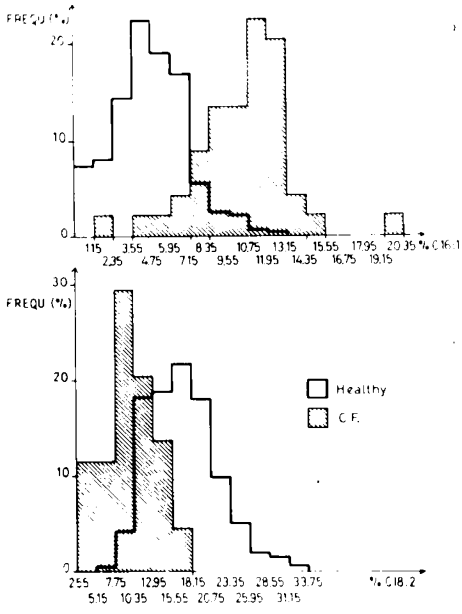
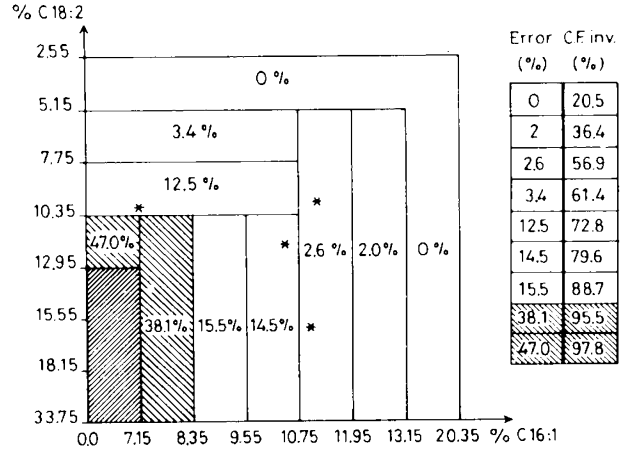


Fig. 2 : Distribution of palmitoleic (▵) and linoleic acid (▷) in the plasma NEFA fraction of healthy and C.F. subjects.

n healthy children = 391.

n C.F. children = 44.



Error (%)	C.F. inv. (%)
0	20.5
2	36.4
2.6	56.9
3.4	61.4
12.5	72.8
14.5	79.6
15.5	88.7
38.1	95.5
47.0	97.8

Fig. 3 : Probability of error in recognition of a C.F. pattern.

Each * represents a C.F. child without pancreatic involvement.

" C.F. inv. " = "C.F. patients involved " : means percentage of total C.F. children examined (n = 44), having a typical C.F. pattern with a possible error in recognition as indicated under " (%) error ".

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