

## ADIPOSIS DOLOROSA ASSOCIATED WITH DEFECTS OF LIPID METABOLISM

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**Abstract.** In two cases with adiposis dolorosa Dercum the fatty acid biosynthesis had been studied with the aid of gas radiochromatography after incubation with acetate-<sup>14</sup>C.

A defective synthesis of mono-unsaturated fatty acids was found in the painful adipose tissue of Case A in comparison with the normal adipose tissue. The results indicate a partial block here of fatty acid synthesis. In Case B the gas chromatogram shows that the major part of the radioactivity is incorporated in C<sub>18</sub> fatty acids indicating a complete block in the endogen biosynthesis of C<sub>18</sub> fatty acids.

A defect of long-chain fatty acid utilization was considered a possible explanation for the progressive adipositas.

Preliminary data obtained with X-ray diffraction analysis suggest an abnormal composition of the triglycerides in the painful adipose tissue compared to that in normal adipose tissue.

In 1892 Dercum described 3 patients with a syndrome which he termed adiposis dolorosa (3). The first known victim of the disease, however, was probably recorded as early as 1500 B.C. by an Egyptian artist. It was the fat Queen of Punt (16). The largest material, a series of 112 cases with juxta-articular adiposis dolorosa has been described by Kling (12). Gram reviewed 69 patients with a triad of adiposis dolorosa, arthritis genuum and arterial hypertension (7). Altogether about 400 cases with somewhat varying symptoms have been described in the literature. The four cardinal signs of the syndrome are:

1. Painful circumscribed or diffuse fatty deposits, often localized to the lower legs. The pain might vary from tenderness-to-pressure to violent attacks of spontaneous pain.

2. Generalized obesity of women, usually menopausal. Only a few men have been described.

3. Asthenia, weakness and often marked fatigability.

4. Psychic phenomena including emotional instability, melancholia, epilepsy, mental confusion, and true dementia.

In addition, the following symptoms have often been described: parasthesias and areas of anesthesia, flushing and cyanosis of the skin, leg ulcers, myxedema, hypertension, epistaxis and arthropathies.

The etiology of the disorder remains unknown. Endocrine dysfunction has been reported in patients with adiposis dolorosa, but the findings are inconsistent. Dercum assumed that the pain was due to neuritis since he found a connective tissue infiltration around the nerves in the fatty deposits (4). Others have found only normal fat tissue upon histological examination (12, 13, 15). An increase of cellular infiltration around the vessels with proliferation of connective tissue has been reported (11) as well as single giant cells (10). Chemical examination of fat from the legs of a patient with Dercum's disease was made by Edsall in 1902 and Page in 1930. The simple methods available at that time revealed no difference from normal fat (5, 15).

We have had the opportunity to investigate some aspects of the fat metabolism in 2 patients with adiposis dolorosa. A study of the biosynthesis of fatty acids from acetate-1-<sup>14</sup>C in the painful adipose tissue revealed a defective formation of mono-unsaturated fatty acids compared with nor-

mal adipose tissue. The excretion of  $^{14}\text{CO}_2$  in the expired air after feeding of oleic acid- $1\text{-}^{14}\text{C}$  showed a decreased oxidation as compared with normal controls. A distinct difference between normal and affected adipose tissue was revealed by X-ray diffraction analyses.

## CASE REPORTS

### Case A

A 42-year-old woman was admitted to the University Hospital in Uppsala on November 19, 1966, with a diagnosis of Dercum's disease. She had healthy, unrelated parents. Since childhood she had been treated with phenobarbital for epileptiform seizures of the grand mal type. Lung tuberculosis was discovered in 1951, symptom-free since 1959. Cholecystectomy in 1958 and renal stones during the following 2 years. In 1961 an increase in weight from 62 to 78 kg during her fourth pregnancy. Thereafter an increase in weight, during 1964 to 85 kg. After otitis she then developed psoriasis of the scalp and knees. Fatty swellings over the knee joints with severe pain especially during the nights. The overlying skin was cold and cyanotic. Parasthesia of the feet, and headache were common when the pain increased. She was very tired and developed an increasing asthenia. In 1965-66 removal of a lipoma around the knees and the maleolar area. Histological examination revealed normal skin and a lobulated lipoma. The severe pain of the legs increased again in 1966. Emotional disturbances with anorexia and frequent vomiting after eating occurred. Her weight reduced to 73 kg. Analgetics, sedatives and vasodilating drugs were of no value. Only during continuous epidural-lumbar anesthesia was she completely free from pain.

Physical examination revealed an obese woman with a pulse of 60, blood pressure 140/70, height 157 cm and weight 73 kg. Several painful soft lipomas on the legs could be palpated on the medial side of both knees and ankles. Some painful infiltrations could also be palpated on the right thigh and scapula region. Healed scars after removal of lipomas and pronounced livedo reticularis was seen on both legs. The legs felt cold up to 2 dm above the knees. This was confirmed by measurements of skin temperature. The mean temperature at the right ankle was 28°C and 29.5°C at the knee region. The left was 1° warmer. Two and 3 dm above the knee it was 31.6°C respectively 35°C on both sides. Ophthalmological, neurological and gynecological examinations were normal.

X-ray of heart, lung, legs, cranium and sella turcica normal. E.E.G. showed a pathological paroxysmal abnormality of an epileptogenic subcortical type. Echoencephalography normal.

*Laboratory tests.* All regular laboratory studies showed normal results including hemoglobin, thrombocytes, WBC, differential count, analysis of urine, sedimentation rate, serum electrophoresis, glucose tolerance test, GOT, GPT, bilirubin, galactose test, alkaline phosphatase, urea, creatinine, electrolytes, fecal fats, and urine analysis. Serum lipids, cholesterol (256 mg%), triglycerides (159 mg%) and free fatty acids showed normal values and response to prolonged fasting.

*Endocrinological examination.* The thyroid function was normal as determined by analysis of protein-bound iodine (4.0-4.7  $\mu\text{g}/100\text{ ml}$ ) and BMB. Stimulation of the adrenals with ACTH showed normal functions. Urine analysis of estron, estradiol, estriol, pregnandiol, FSH, LH, 17-hydroxycorticosteroids and 17-ketosteroids were normal.

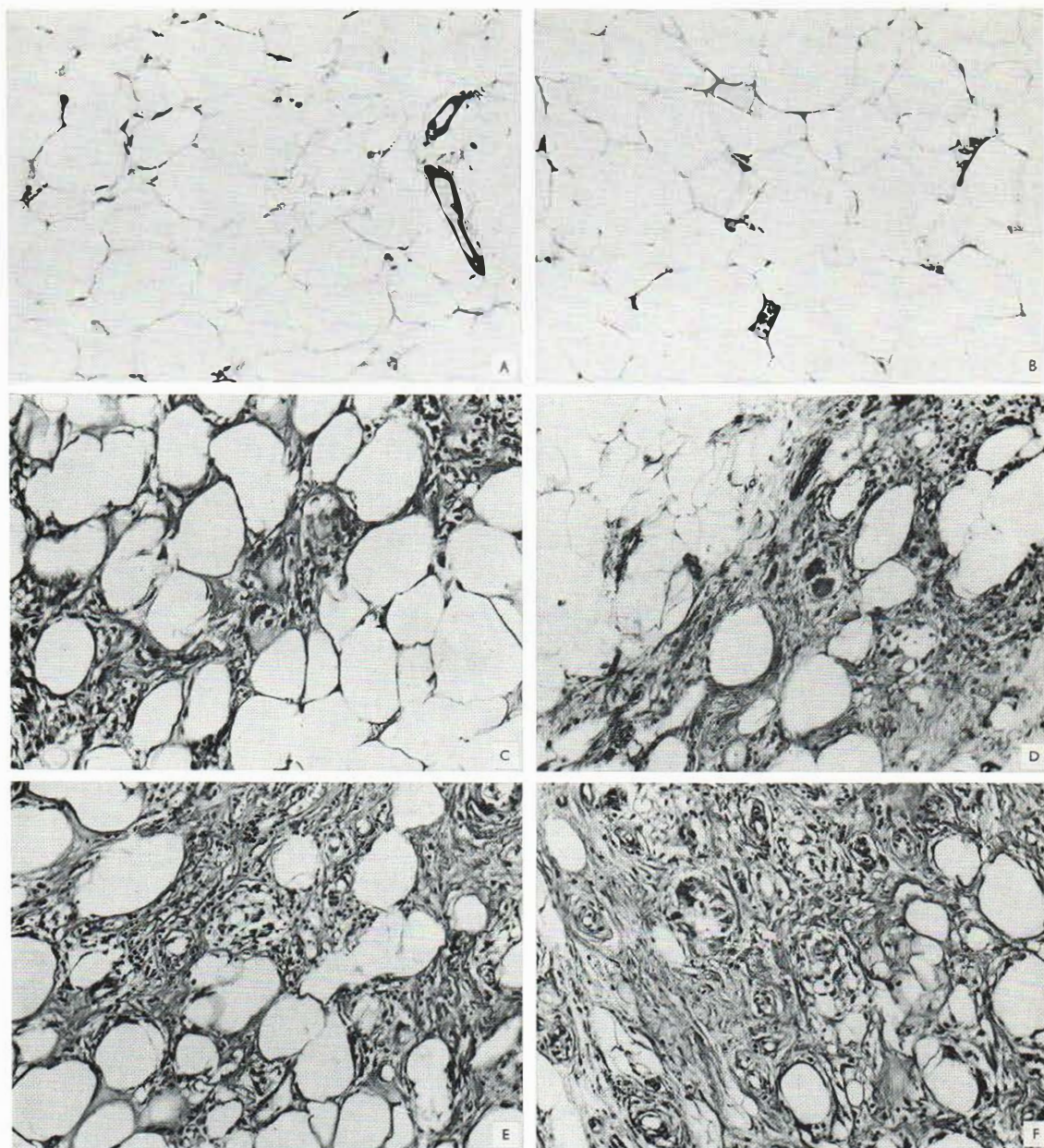
### Case B

A 46-year-old housewife with three children, ages 16 to 21 years. In 1963 attacks of cholecystitis and cholecystectomy was carried out. Since then, often gastritis. Her weight increased during following 3 years from 56 kg to 86 kg. Treated with diuretics without effect. She then also developed painful infiltrations of both lower legs which were very sensitive to pressure. She also had parasthesia when walking. She is very tired, cannot work and cries often. When the patient was first seen in January, 1967, she had a 5 × 6 cm red-violet infiltrate with a central, pea-sized ulcer on the left leg above the ankle. Both legs were swollen below the knees and very painful to palpation. Her weight was 94.4 kg and height 164 cm. The obesity was especially obvious over the abdomen, buttocks and legs. Her blood pressure was 140/90. Pulse normal. X-ray of heart, lung, total skeleton including cranium and sella turcica normal. There were no signs of myeloma. ECG and E.E.C., skin temperature measurements, gynecological examination as well as those of eyes, ears, nose and throat were normal.

*Laboratory findings.* The same laboratory studies as in case A were carried out. They all revealed normal values with the exception of serum electrophoresis. Here an abnormal, distinct protein fraction was seen on paper electrophoresis. The serum was fractionated by a thin layer gel-filtration technique (1), and the abnormal fraction was shown to be an IgG globulin (7S). Bone marrow normal. Cryoglobulins negative. Urine electrophoresis was normal. Triglycerides were 100 mg% and cholesterol 260 mg%. Determination of fecal fat showed normal values. Antibodies to liver, kidney and thyroid gland negative.

## MATERIAL AND METHODS

Biopsies of case A were obtained from the painful subcutaneous tissue of the left leg and of normal non-affected adipose tissues from two different places at the left leg. In case B biopsies were obtained from the non-painful abdominal adipose tissue, from painful infiltrates in the front of both lower legs and the back of the right leg. One part was taken for patho-anatomical study (Fig. 1) and the rest, about 1 g, was immediately placed in pre-cooled Krebs-Ringer phosphate buffer. All incubations were started within 10 min of obtaining the biopsy. The tissue was cut into small pieces with a razor blade. The slices were then transferred to a 50 ml Erlenmeyer flask together with 5 ml of Krebs-Ringer phosphate buffer and 0.5 mCi acetate- $1\text{-}^{14}\text{C}$  (spec. act. 44.4 mCi/mM, The Radiochemical Centre, Amersham, England). The flasks were incubated for 2 hours at 30° in a shaking water bath and flushed with 95%  $\text{O}_2$  + 5%  $\text{CO}_2$ . The incubations were terminated by placing the flasks in boiling water and the tissue was washed with saline three times.



*Fig. 1a.* (A-B) Normal adipose tissue from case A. Delicate fibrous strands with thin collagen fibers. The fatty content of the individual cells is completely dissolved. (C-F) Adipose tissue from four painful noduli. The fatty

content in some lobuli is incompletely dissolved. Formation of granuloma with foreign-body giant cells, infiltration of lymphocytes and increase of the interstitial collagen.

Total lipids were extracted with chloroform methanol (2:1, v/v) and the total lipid extract as re-extracted with hexane. The triglycerides from the adipose tissue were purified by silicic acid chromatography. The purity was tested with thin layer chromatography.

The radio assay was performed by liquid scintillation counting with a Tri-Carb Spectrometer.

Methyl esters were formed by transesterification with 1% sulphuric acid in methanol/benzene (2:1, v/v).

For simultaneous determination of mass and radioactivity in the triglyceride fatty acids, a preparative Pye Argon chromatograph equipped with a strontium detector and a Pyrex glass effluent splitter was used (2).

Separate mass analyses were also performed with an

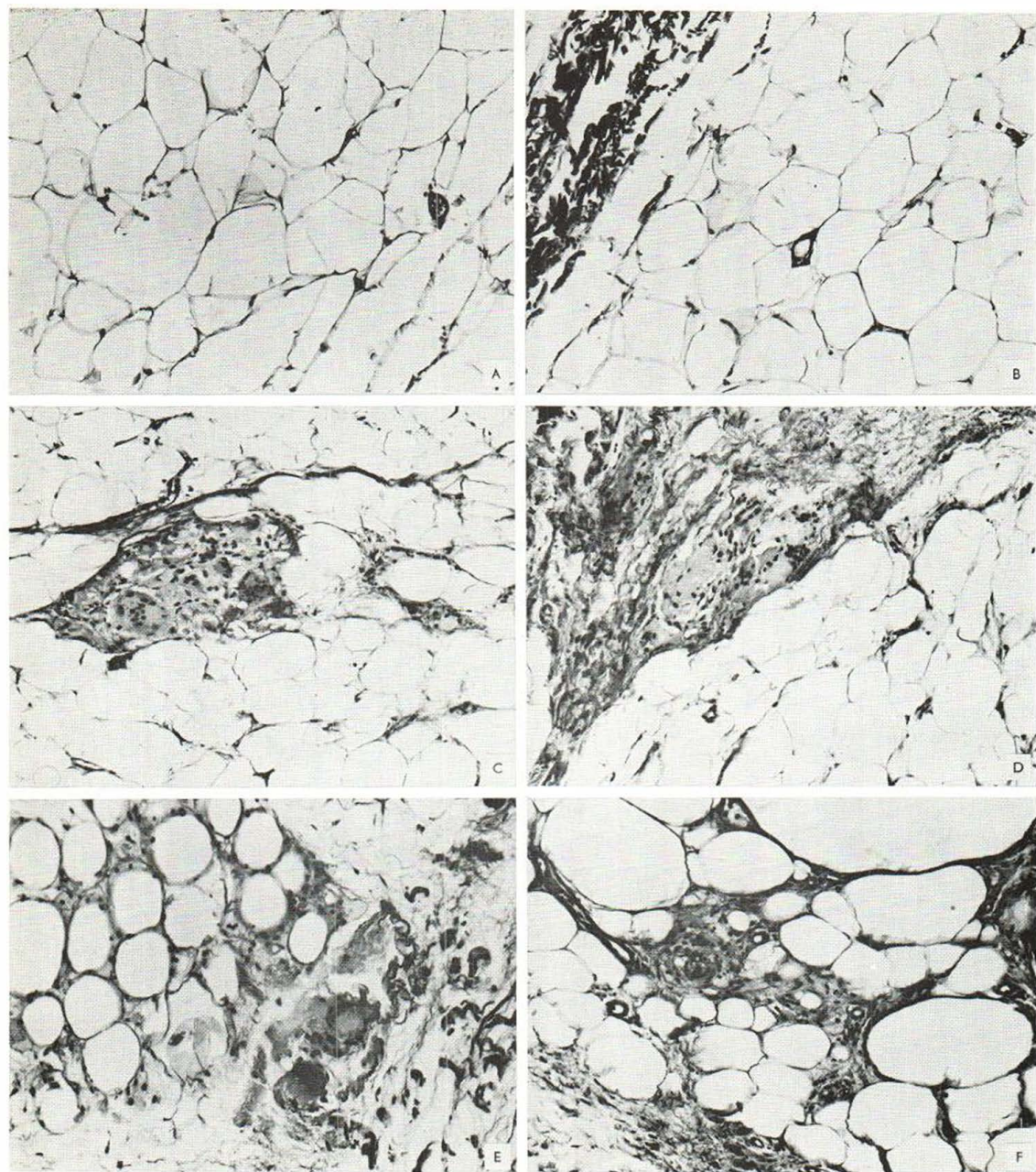


Fig. 1b. Normal adipose tissue from abdomen of case B (A-B) and painful adipose tissue from front of both lower legs (C-D) and the back of right leg (E-F) with

the same changes as in case A. All sections stained with hematoxylin and eosin,  $\times 113$ .

analytical Perkin-Elmer 801 gas chromatograph (flare ionization detector), using a 4 m glass column with 1.2% EGSS-X on Celite to check the analyses of the fatty acid methyl esters.

X-ray diffraction analyses and NMR-analyses of the *Acta Dermatovener (Stockholm) 51*

triglyceride structure was carried out according to Ohlsson (14).

*Radiospirometry.* In the morning the subjects were fed 5 g oleic acid- $1^{14}\text{C}$  in 150 ml skim milk after fasting for 12 hours. The excretion of  $^{14}\text{CO}_2$  in expired air

was registered with a radiorespirometer FHT 50 (Friesecke & Hoepfner). The instrument was calibrated with  $^{14}\text{CO}_2$  generated from  $\text{Ba}^{14}\text{CO}_3$ . The excretion of  $^{14}\text{CO}_2$  in expired air was assayed continuously for the first 3 hours and then in 45-min periods, with 45-min intervals, for 12 hours. The excretion of  $^{14}\text{CO}_2$  was assayed and expressed as per cent per minute of the given dose. These values were plotted in a linear system against time. The cumulative expired radioactivity was estimated by weighing the area under the curve.

**RESULTS AND COMMENTS**

Histological examination of the biopsies revealed significant differences between painful and non-painful adipose tissue. In the painful tissue there was an incomplete dissolution of fat and granuloma formation with giant cells suggesting a reaction similar to foreign body reaction (Fig. 1).

The composition of the triglyceride fatty acids of normal adipose tissue and painful adipose tissues is given for cases A and B in Tables I and

Table I. *Composition of fatty acids in triglycerides of normal adipose tissue and painful adipose tissue from case A with Adiposis dolorosa Dercum*

The analyses were carried out with a Perkin-Elmer 801 using DEGS and Se30

	Normal control	Painful adipose tissue
<i>GLC</i>	<i>DEGS</i>	<i>DEGS</i>
C12:0	0.8	1.2
C12:1 + (13:0)	0.2	0.3
C14:0	3.8	4.1
C14:1 + 15:0	2.0	2.0
C16:br?	0.2	Traces
C16:0	14.8	16.1
(C17:0) + 16:1	13.6	12.5
C16:2 + 17:1	0.2	0.3
C18:0	0.5	0.8
(C17:2) + 18:1	50.9	49.1
C18:2	7.5	8.4
C20:0	0.2	Traces
C18:3 + 20:1	3.9	4.1
C22:0 +	0.3	0.2
C22:1	1.2	0.7
	<i>Se30</i>	<i>Se30</i>
C12	1.0	1.4
C14	4.7	5.3
C15	0.7	0.6
C16	27.5	26.3
C17	1.1	1.5
C18	59.2	59.4
C20	3.8	4.0
C22	1.8	1.6
C24	Traces	

Table II. *Composition of fatty acids in triglycerides of normal adipose tissue and painful adipose tissue from case B with Adiposis dolorosa Dercum*

The analyses were carried out with a Perkin-Elmer 801 using 3% EGSS-X

	Normal control	Painful adipose tissue
<i>GLC</i>	<i>Egss-x</i>	<i>Egss-x</i>
C12:0	1.33	1.25
C14:0	5.12	4.17
C14:1	1.09	1.17
C16:br?	0.31	Traces
C16:0	17.81	17.78
C16:1	9.89	9.48
C18:0	2.32	3.47
C18:1	46.09	48.84
C18:2	10.11	9.43
C18:3 + 20:0	2.22	1.80
C20:1	1.93	1.58
C22:0	0.33	0.47
C20:4	0.76	Traces
C(22:1)	0.61	0.51

II. There are no striking differences between the painful and non-painful adipose tissue.

Photographs of the original recorder tracings of the gas radiochromatograms of fatty acids in triglycerides are shown for case A in Figs. 2 and 3. The fatty acids pattern as well as the distribution of the activity in the fatty acids are shown in these figures. A comparison of the two gas radiochromatograms indicates that there is a difference in the formation of mono-unsaturated fatty acids (16:1 and 18:1) in the affected adipose tissue (Table III).

For case B the gas radiochromatograms of painful adipose tissue indicate a synthesis of  $\text{C}_{16}$  fatty acids, but a complete block in the synthesis of  $\text{C}_{18}$  fatty acids (Fig. 4).

Preliminary structural studies of the glycerides of the adipose tissue with the aid of X-ray diffraction and NMR analyses revealed distinct differences (Figs. 5 and 6). The underlying structural difference is not yet known, but these preliminary analyses suggest the presence in the painful adipose tissue of glycerides with abnormal distribution of the fatty acids.

The oxidation of ingested oleic acid-1- $^{14}\text{C}$  was studied with the aid of radiorespirometry. The excretion  $^{14}\text{CO}_2$  in the expired air was measured, and expressed as a percentage of the administered

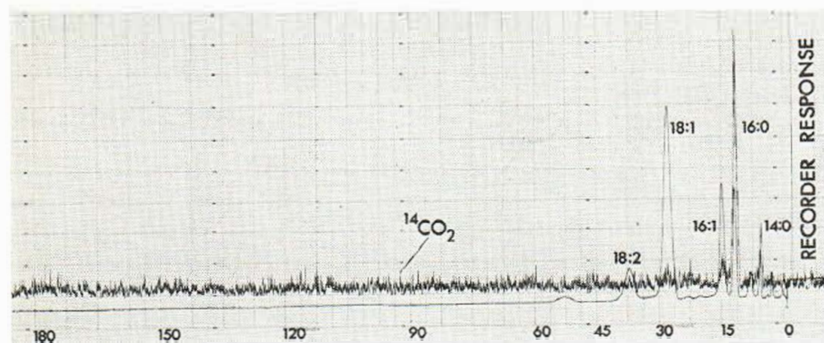


Fig. 2. Gas radiochromatogram of fatty acids biosynthesized by normal adipose tissue of case A after incubation with acetate-1- $^{14}\text{C}$ .

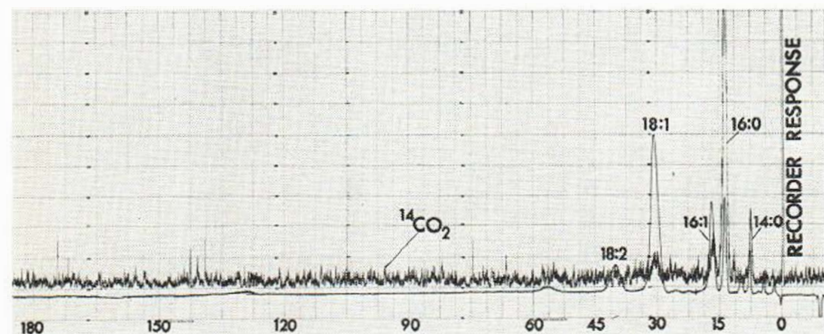


Fig. 3. Gas radiochromatogram of fatty acids biosynthesized by painful adipose tissue of case A after incubation with acetate-1- $^{14}\text{C}$ .

Table III. Distribution of radioactivity in the different fatty acids of normal and painful adipose tissue after incubation with acetate-1- $^{14}\text{C}$  (case A)

	Per cent of total radioactivity found in the different fatty acids				
	12:0	14:0	16:0	16:1	18:1
Normal adipose tissue		11.2	63.5	13.7	11.6
Painful adipose tissue		13.5	67.3	11.6	7.6

dose (Fig. 7). As can be seen from this figure there is a significant difference in the amount of the oxidation to  $^{14}\text{CO}_2$  of oleic acid-1- $^{14}\text{C}$  in nor-

mal controls and in the patients with adiposis dolorosa.

Thin layer chromatography on silica plates of painful fat tissue showed the same pattern as the normal fat tissue.

During recent years it has been shown that adipose tissue is a metabolically active and hormonally responsive tissue. Different techniques have been extensively applied to the adipose tissue in the rat in order to elucidate the metabolic pathway of the fat cell. By contrast, information on the adipose tissue of man is still limited. Slices of human subcutaneous or omenthal adipose tissue convert glucose to  $\text{CO}_2$ , glyceride glycerol and

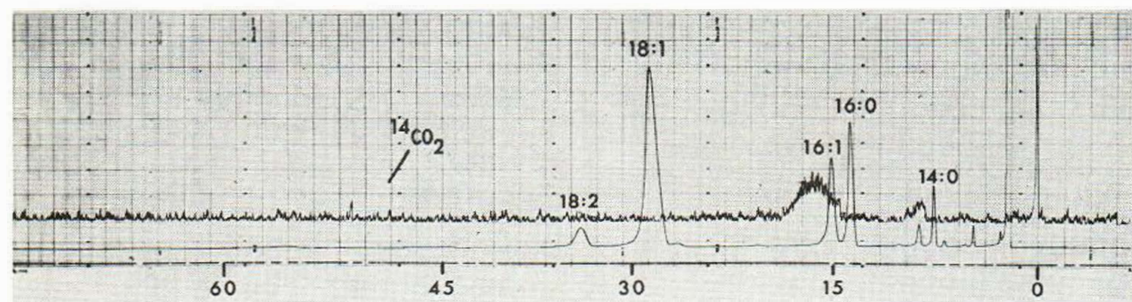


Fig. 4. Gas radiochromatogram of fatty acids biosynthesized by painful adipose tissue of case B after incubation with acetate-1- $^{14}\text{C}$ , indicating a synthesis of  $\text{C}_{10}$  fatty

acids and a complete block in the synthesis of  $\text{C}_{18}$  fatty acids.

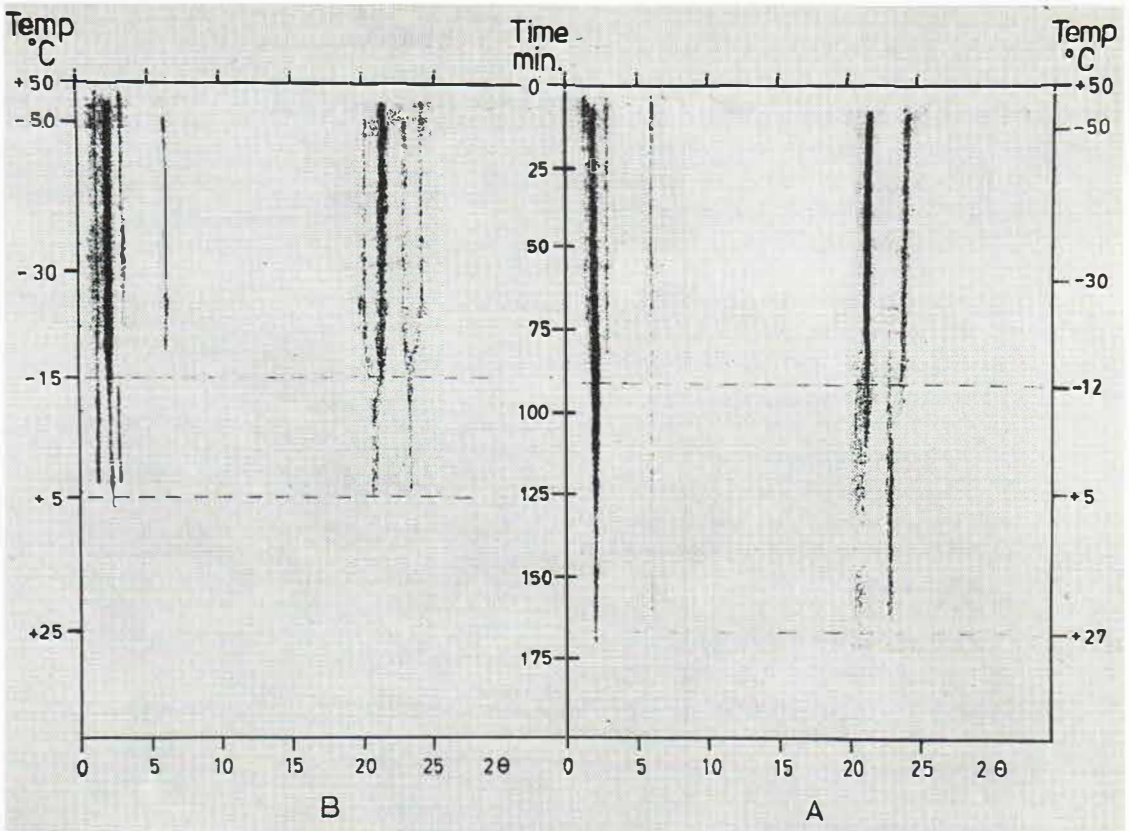


Fig. 5. Roentgen diffraction analyses of triglycerides from case B with a DPT-camera. A) Normal adipose tissue. Cooling at a rate of 0.3°C/min results in two different

curves, with more diffuse short-spaced lines in the fat from the painful adipose tissue. (B) Painful adipose tissue.

glyceride fatty acids. Acetate is also converted to glyceride fatty acids (6, 8, 9).

No detailed information is available in the literature about the formation of the individual

fatty acids in the normal human adipose tissue or other pathological conditions.

We have analysed the biosynthesis of fatty acids in adipose tissue from five normal controls

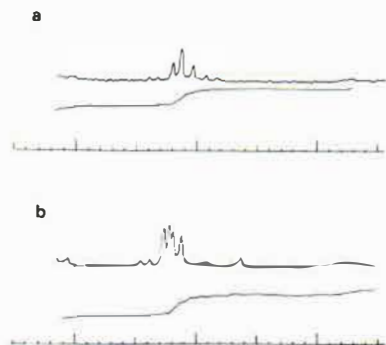


Fig. 6. (a) The NMR spectrum of triglycerides from normal adipose tissue (case B). (b) The NMR spectrum of triglycerides from "painful" adipose tissue (case B).

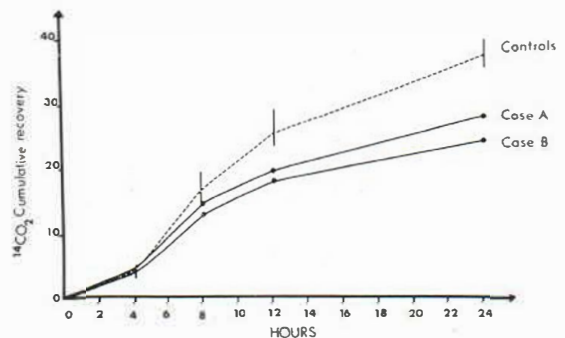


Fig. 7. Excretion of  $^{14}\text{CO}_2$  in expired air after feeding oleic acid- $1\text{-}^{14}\text{C}$  to 2 cases of adiposis dolorosa, compared with 5 normal controls.

(unpublished observations). The biosynthetic pattern of fatty acids is the same as in the normal tissue from the case with Dercum's disease. In the painful adipose tissue from patients with adipositis dolorosa Dercum, there was a striking difference in the endogenous biosynthesis of fatty acids with a partial block in case A and, in case B, a complete block in the synthesis of C<sub>18</sub> fatty acids.

In the present report clinical, metabolic and morphologic studies suggest that the intermittent attacks of painful adipose tissue result from local defects in lipid metabolism. The progressive adipositis observed might be due to a defect in utilization of long-chain fatty acids.

Whether the abnormal protein fraction observed in one of the cases is associated with the defect lipid metabolism is difficult to evaluate at present.

Potential enzyme defects in our two patients remain to be located more precisely. These descriptions of a possible defect in the biosynthesis of long-chain fatty acids, the presence in the painful adipose tissue of glycerides with abnormal distribution of the fatty acids, and a defect in the utilization of dietary long-chain fatty acids may be of value in the evaluation of other still undefined relations between adipositis and defects in primary energy sources.

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