SCLEREMA NEONATORUM AND ITS RELATION TO FAT NECROSIS.

REPORT OF A CASE BY

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Sclerema neonatorum is a rare disease of early infancy, characterized by swellings in the subcutaneous fat, of characteristic distribution—on the back, shoulders, buttocks, and cheeks. In these lesions the fat crystallizes out during life, probably as neutral fat, and in well-marked cases the crystals give rise to an inflammatory reaction of the “foreign body” type, with giant cells. In these cases also, calcium is deposited in the lesions.

The histological and chemical work described in this paper was undertaken by one of us (F.K.H.) at the suggestion of Dr. G. A. Harrison, and is on the same lines as his own investigations on sclerema neonatorum ⁽¹⁾ ⁽²⁾.

I. CLINICAL RECORD (G.L.S.K.).

An infant girl, aged 2 weeks, was admitted to Paddington Green Children's Hospital, under Dr. Sutherland's care, suffering from frequent convulsions. The child had been born at full term by an instrumental labour, had been partially asphyxiated at birth, and had weighed 8 lbs. It had been given the breast for the first 3 days, and later Allenbury's Food, but had never taken the feeds well. A red rash had appeared at the age of 9 days, and had gradually spread over the body.

There was nothing abnormal in the family history.

On examination the infant was small and poorly nourished. Convulsions were taking place about every half hour, the arms, legs, and face showing clonic contractions. The fits were chiefly right-sided, and the right leg was somewhat spastic. The knee jerks were equal and active; the neck muscles were not rigid; the pupils were equal, but reacted sluggishly to light, and there was no strabismus. A dark red morbilliform eruption was present on the trunk, limbs, and face. There were petechiæ on the back, and in the mucous membrane of the hard palate. There was considerable peeling of the skin around the mouth, and the nails of the fingers and toes, but practically none on the palms of the hands.

Over considerable areas the skin and subcutaneous tissues were indurated, and of uneven surface on palpation. The skin could not be pinched up over these areas, but the subcutaneous tissue was freely movable on the deeper structures. The induration was present over the greater part of the dorsum of the thorax, and the skin over this area was purplish in colour, and the capillary circulation poor. There was a cyst of about $\frac{3}{4}$ -in. in diameter near the inferior angle of the right scapula. Other indurated areas were present over both deltoids, the lateral and proximal portions of the thighs, and on both buttocks, where the induration seemed to be deeper seated, and where there was ulceration of the overlying skin. There was also an area of induration of about 1-in. in diameter over the right zygoma; this area was umbilicated, and shewed central softening, and, like the other nodules, was movable on the deeper structures. The distal segments of the limbs were free from induration, except for a few nodules over the extensor surface of the right forearm.

The lower border of the liver could be felt in the right nipple line at the umbilical plane, but it could easily be displaced to the subcostal plane by pressure. The gall bladder was easily palpable, and very tense. The spleen could not be felt.

While the infant was in hospital her condition fluctuated considerably. The temperature varied between 96° and 101.2°. For the greater part of the time the temperature was raised or normal. On 6 occasions only it fell as low as 96° F. Three days after admission the convulsions had ceased and the rash had disappeared; the petechiæ increased in number before finally vanishing. The child died 21 days after admission. Vomiting occurred during the last 5 days. The Wassermann reaction was negative. A radiological examination was made post mortem, and shewed no opacities in the subcutaneous tissues, but this may have been due to the use of too hard a ray.

Post Mortem Examination. Weight, 6 lb. 4 oz. There was fine desquamation of the skin over the whole body, and especially on the back.

The firm, indurated nodules in the subcutaneous tissue have already been described. In these areas the fat had the appearance of lard and was of firm consistency. Elsewhere the subcutaneous fat was small in amount. The cyst near the inferior angle of the scapula contained a small quantity of thick creamy material, which microscopically shewed a few tufts of acicular crystals. There was another small cyst, the size of a pea, in the indurated tissue over the left deltoid. The perinephric fat was small in amount but was also white in colour. The liver was slightly enlarged and engorged, and shewed ptosis. The other organs shewed no macroscopic change.

Histological Examination The *pancreas* shewed some post-mortem autolysis, but no pathological change. In the *liver* there was marked engorgement of the sinusoids. The parenchyma cells shewed cloudy swelling, and in places fatty degeneration. The *kidneys* shewed moderate hyperæmia. Hyaline thrombi were present in the glomeruli, which were adherent to the Bowman's capsules. There was an exudate of serum into the Bowman's capsules of some glomeruli. The tubular epithelium shewed marked degeneration, with vacuolation. In the *suprarenals* there was marked hyperæmia of the deeper layers of the cortex.

I wish to express my thanks to Dr. G. A. Sutherland for allowing me to publish this case.

II. HISTOLOGICAL AND CHEMICAL EXAMINATION. (F.K.H.).

1. HISTOLOGY OF THE SUBCUTANEOUS TISSUES.

Paraffin sections. There is no pathological change in the cutis. In the subcutaneous tissue, many of the fat cells contain an eosin-staining substance, in which may be seen clefts, left by the solution of crystals. The clefts appear as fine radiating lines, radiating sometimes from a point in the centre of the fat cell, but usually from a point near the periphery. The arrangement of the clefts is exactly similar to the arrangement of the crystals seen in frozen sections. There are no clefts in the interstitial tissue.

No signs of calcification are found. There is some inflammatory reaction but it is not marked. The cells present are all young fibroblasts and mononuclear cells. There are no giant cells.

Frozen sections. The fat globules are filled with tufts of long, anisotropic, acicular crystals, which do not extend outside the fat cells. The contents of the fat cells stain red with Sudan III and pink with Nile blue sulphate. If a section stained by Nile blue is heated on the warm stage until the crystals melt, the pink staining becomes more intense than in the unheated section. The solid crystals themselves are presumably unstained, though, as viewed with the crossed Nicol's prisms, the light passing through them shews the colour of the surrounding stained fat.

The melting point of the crystals, and their solubility in various solvents, have been determined, using the polarising microscope and a warm stage. The crystals melt at 50-56° C. On cooling the section, they begin to reappear at 30° C. There is no liquid crystal formation,

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Solubility of the crystals. In *alcoholic soda* (N/2 NaOH) the crystals are insoluble at room temperature, and dissolve at 45° C. In *alcohol* (absolute) the majority of the crystals disappear at 45° and over. All disappear below 60°. In *ether*, if by evaporation of the solvent the section is allowed to cool below room temperature, the crystals do not appear soluble, but they dissolve at once when placed on the warm stage at 25° C. (The actual temperature of the section would no doubt be lower than this, owing to evaporation of the ether.) In *petroleum ether*, the crystals dissolve at once on the warm stage at 25° C. They are also soluble on heating in *acetone* and *benzene*.

Benda's reaction. This is a test for the presence of free fatty acids and soaps. Small pieces of tissue, hardened in formol, are treated with a mixture of copper acetate, acetic acid, and chrome alum. If fatty acids or soaps are present, the copper combines with them to form copper soaps, which form conspicuous green masses visible to the naked eye, and appear in frozen sections as tufts of green acicular anisotropic crystals. The reaction is negative in this case.

Melting point of the crystals in sclerema. The appearance of anisotropic acicular crystals in the fat globules in frozen sections of fatty tissues, and of organs shewing fatty degeneration, is very common. This is of importance, since the appearance of acicular crystals has often been assumed to imply the presence of free fatty acids. This is an unjustifiable assumption; the presence of crystals is not in itself pathological.

It is therefore of interest to compare the melting points of the crystals in normal infants' subcutaneous fat, and in sclerema. This has been done by Harrison⁽¹⁾, who found that the melting point of the crystals in sclerema was higher than that of the normal crystals. He has given me the opportunity of making further observations on his material, using the polarising microscope and warm stage; the results are given in Table I.

TABLE I.

CASE	Crystals melt at :	Crystals reappear at :
Harrison : Case III. (1) Short crystals, of general distribution. . (2) Tufts of long acicular crystals.	31°-34° C. Not melted at 60° C.	21° C.
Harrison : Case IV. All crystals alike.	43°-62° C.	47° C. and under.
Present Case All crystals alike.	50°-56° C.	30° C.
Normal Infant (aged 1 wk.) Subcutaneous fat.	31°-37° C.	23°-21° C.

In making these observations it is necessary to raise the temperature of the warm stage very gradually, keeping it steady at a given temperature until it is evident that there are crystals present which will not disappear. Even when this is carefully done, the melting points are not sharp; for example, in Case IV, although some crystals began to melt at 43° C., there were others which were not melted when the temperature was steady at 59° C. Yet there

was no sharp distinction between the crystals of the lower and higher melting points. In this case, crystals were present both within and without the fat globules, and, upon the whole, the extracellular crystals had a higher melting point than the intracellular crystals.

In Case III there were two distinct types of crystal. Some were fine short rods with a melting point practically identical with that of the crystals in normal fat. These would not be present during life and are not pathological. Other crystals were present—the long crystals arranged in tufts—with a melting point above 60°C ., which was the limit to which the warm stage could be taken. These crystals were certainly present during life, and would account for the inflammatory reaction with giant cells, characteristic of the response to irritation by a foreign body.

The determination of the melting points gives little help in identifying the crystals, but it does serve to distinguish the crystals which were present during life, and to demonstrate the difference between the normal and sclerematous fat. In the case described in this paper, it cannot be definitely said that the crystals were present during life: although they required a temperature of 50° — 56°C . to melt them, they did not reappear until cooled to 30°C ., and therefore may have been present in the liquid state at body temperature. Nevertheless, there is an abnormality in the fat, since the melting point of the crystals is higher than that of the crystals in normal fat.

The question of saponification. Since a number of cases, apparently identical with sclerema, have been reported as cases of subcutaneous "fat necrosis," it was a point of special interest to determine whether hydrolysis or saponification occurs in sclerema. Harrison^{(1) (2)} considered that there was no appreciable liberation of free fatty acids in his cases, and that certainly the crystals were not fatty acids, but probably neutral fats. This opinion was based (a) on the microchemical finding, that the crystals in frozen sections were not soluble in alcoholic soda in the cold, and only disappeared on heating above their melting point: and (b) on chemical evidence, that the acid values of the ether extracts of sclerematous tissue, though higher than the normal values, were far lower than would have been expected if the crystals present in the sections had been fatty acid crystals. My own histological and chemical results confirm this view. This histological evidence against saponification is:—(1) failure of the crystals to dissolve in cold alcoholic soda; (2) negative Benda's reaction: and (3) absence of any evidence of soap or free fatty acid in sections stained by Nile blue sulphate even when the crystals are melted.

The case described in this paper seems to be at an earlier stage than those described by Harrison. There are no crystals outside the fat cells, and therefore no "foreign body" reaction, and there is no microscopic evidence of calcification.

2. CHEMICAL INVESTIGATION OF THE PRESENT CASE.

Methods. The subcutaneous fat from the affected regions was divided into two portions. The first, (A), was cut up into small pieces, spread on a watch-glass, and dried to constant weight in a vacuum dessicator. The second, (B), was cut up and dried by grinding with sand and anhydrous sodium sulphate to form a powdery mixture. Both samples were extracted with ether, for 3 to 4 days, in a Soxhlet apparatus. The ether soluble portion after evaporation of the

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ether (the "ether extract") was stored in a vacuum dessicator over CaCl_2 and paraffin shavings until constant weight was reached. The ether insoluble portion ("ether-extracted residue") from (A) was similarly stored.

Drying without sodium sulphate is very slow, and much hydrolysis may occur while the tissue is in the dessicator. The ether extract from fat so treated is therefore unsuitable for determinations of the acid value. But since an "ether-extracted residue" free from contamination was required for the determination of calcium and of soaps, the fat had to be divided into two samples as described above. The "ether extract" from (B) was used for the determination of the melting point, acid value, saponification value, and iodine value; the "ether extracted residue" from (A) was used for determinations of calcium and soaps.

Ether extract. The melting point was estimated by the open capillary method; the acid value and saponification values by the usual standard methods, and the iodine value by Wij's method.

Cholesterol was not estimated. The chloroform solution of the fat gave a brown colour with the acetic anhydride and sulphuric acid, which made colorimetric methods (Myers & Wardell) impossible, and there was not enough material available for the digitonin method.

Ether-extracted residue. Total Calcium was estimated in the ash of the tissue by Kramer & Tisdall's method.

Soaps. The soaps of Ca, K, and Na are soluble in amyl alcohol (Maver & Wells, (3)). To determine the amount of calcium present as soap (if any), the ether-extracted residue was extracted with amyl alcohol in a Soxhlet apparatus heated on a sand bath (8 to 9 hours). The amyl alcohol was evaporated to small volume and the solution transferred to a crucible. The remainder of the amyl alcohol was driven off by heating on a sand bath and the residue ashed in a furnace. No ash remained. This excludes sodium and potassium soaps as well as calcium soaps.

The efficiency of the amyl alcohol extraction was checked by testing the method with calcium palmitate, which was extracted completely under the same conditions.

The results are given in Table II.

TABLE II.

	Ether Extract				Ether Extracted Residue	
	Melting point	Acid Value : mgm.KOH per 1 gm. fat	Saponification Value : mgm.KOH per 1 gm. fat	Iodine Value : gm. iodine per 100 gm. fat	Total Calcium : % of residue	Soap
Sclerema	47° C.	2.7	209	46.7	.66%	Absent
Normal	23° to 44.6° C.	0.9 to 2.7	190 to 206	46.7 (average)	.072%	—

The normal figures are here taken from Harrison's paper.⁽¹⁾ Those for the acid value, saponification value, and total calcium are his own figures. The iodine value is an average of very variable figures collected from the literature for children of 1—2 months.* Harrison's series of normal controls does not include a case as young as ours, and it is necessary to compare children of the same age, since the iodine value increases with age.

The figures show no hydrolysis or saponification of the fat: the free fatty acid is not increased and no soap was found.

* The figure given as normal was obtained on the separated fatty acids, and is therefore not really comparable with my figure. The difference in iodine value between the fat and fatty acids would probably not be more than 5%, and would not be sufficient to bring the figure outside normal limits.

There is, as in Harrison's cases, no change in the iodine value, but, as he has pointed out, this does not disprove the theory that the raised melting point of sclerematous fat is due to a diminished proportion of olein, since the olein might be diminished sufficiently to cause a definite rise in the melting point without producing a significant diminution in the iodine value.

It is of interest that the calcium content of the tissue shews a marked rise, without any microscopic evidence of calcification, and in the absence of calcium soaps. The formation of calcium soap is said to be an important stage in many types of calcification—atheroma, Monckeberg's arterio-sclerosis, calcified fibromata, calcified tuberculous nodules, and pancreatic fat necrosis—and is regarded as the earliest stage in the deposition of calcium (Klotz⁽⁴⁾ ⁽⁵⁾). If sclerema were essentially a "traumatic fat necrosis" associated with saponification, one would expect this method of calcification. Since our case is too early to shew microscopic or radiological evidence of calcification, one cannot lay much stress on the absence of calcium soaps, but there is a marked rise in the calcium content of the tissue without soap formation.

Summary of the results in the present case of sclerema.

- (1) Fat cells contain an eosin-staining substance with clefts left by crystals.
- (2) There is some inflammatory reaction.
- (3) Crystals occur in the frozen sections, of a higher melting point than those in normal fat.
- (4) There is no histological evidence of saponification.
- (5) There is no histological evidence of calcification.
- (6) The fat extracted from the tissues has a raised melting point, but the acid value, saponification value, and iodine value are normal.
- (7) The residue after extraction of the fat has a high calcium content, but contains no soap.

III. TRAUMATIC FAT NECROSIS, AND "ADIPONECROSIS SUBCUTANEA NEONATORUM."

No attempt will be made here to summarize the literature on sclerema neonatorum; a review will be found in Harrison's paper⁽¹⁾. But there are in the literature a number of cases, closely resembling sclerema, and apparently identical with it, described as "traumatic fat necrosis" or "adiponecrosis subcutanea neonatorum."

"Traumatic" or "ischæmic" fat necrosis is a well recognized condition which may occur as a result of injury to fatty tissue. It may occur in any situation, but is commonest in the fat overlying the breast. This remark of course applies only to adults.

Frozen sections of the material shew acicular crystals, and the paraffin sections shew an eosin-staining substance filling some of the fat cells, with radiating crystal-clefts within it. The clefts may also occur in the interstitial tissue. There is a cellular inflammatory reaction, often of the "foreign body" type, with giant cells and "foamy" cells (lipophages). Calcification and fibrosis occur in the late stages.

Cases have been published by Lee and Adair⁽⁶⁾, Farr⁽⁷⁾, Parsons⁽⁸⁾, Lecene and Moulouquet⁽⁹⁾ and Hadfield⁽¹⁰⁾. Evidence of the saponification is given by Farr, and by Lecene and Moulouquet.

Lecene and Moulouquet⁽⁹⁾ described several cases, mostly in women, occurring in the fat overlying the breast. They regarded the process as closely similar to pancreatic fat necrosis, and regarded the saponification as the primary lesion, giving rise to a secondary inflammatory reaction. They demonstrated the presence of saponification by Nile blue staining, and they noted that crystals were present in the normal fat, and that the crystals seen in the necrotic areas had a higher melting point than those in the normal fat.

Farr⁽⁷⁾ produced experimental fat necrosis in the subcutaneous tissue of pigs by trauma, and demonstrated saponification in these cases by means of Benda's reaction and Nile blue staining. His first case of human "ischæmic fat necrosis" occurred in an infant, and, from the clinical and histological description, seems to have been identical with sclerema. It is not clear whether he used Benda's reaction and Nile blue staining in this case.

Cases identical with sclerema have been described as "subcutaneous fat necrosis of the newborn" or "adiponecrosis subcutanea neonatorum" by Bernheim-Karrer⁽¹¹⁾, Carol and Van der Zande⁽¹²⁾ and others. The case described by Carol and Van der Zande supplies evidence that saponification may occur in these cases. They do not regard their case as one of "sclerema," but there has been much confusion in the terminology of the condition, and their case is evidently one of "sclerema" in the sense in which the term is used in this paper. They reserve the term for a more severe disease, with marked constitutional symptoms. Their case is described as follows:—

A boy, born by a normal but prolonged labour, and asphyxiated at birth, seemed normal until the age of 3 weeks, when a lump developed on the back, between the shoulder blades, and spread over the whole upper part of the back. A week later, similar swellings developed over the left shoulder and in both cheeks, and lastly in the buttocks. These swellings were attached to the skin, but movable on the deeper structures; they were firm, not fluctuating, and not tender. The child died in convulsions at the age of 5 weeks.

Sections of the subcutaneous tissue shewed infiltration with lymphocytes, fibroblasts, and giant cells of the foreign body type. The fat cells and their nuclei stained poorly, and the intercellular partitions were oedematous. Many cells were filled with a granular substance shewing star-shaped crystal-clefts, and these clefts were also present in the connective tissue trabeculae.

In frozen sections, tufts of anisotropic acicular crystals were seen. Sections stained by Nile blue shewed some fat cells with pink-stained contents, others with light blue contents, others deep blue. The anisotropic crystals were most conspicuous in the pink cells, and there was no double refraction in the deep blue cells. Corresponding cells could be recognised in sections stained by Fischler's method: the cells which were dark blue with Nile blue were blue-black with Fischler's stain. (Fischler's method is a modification of Benda's, and differs in that the fatty acids and soaps are stained blue-black—see Fischler⁽¹³⁾ and Klotz⁽⁵⁾).

Carol and Van der Zande regard the presence of double refraction as implying the presence of cholesterol esters. This is not convincing. As far as the *crystals* are concerned, the presence of double refraction means little, for so many crystals shew it. Where double refraction appears to occur diffusely in a fat globule, it is necessary to look closely for crystals, as small crystals densely arranged in a fat cell in a thick section may cause the globule

to shew double refraction, and the crystalline structure may not be very obvious. True liquid crystals of cholesterol esters, as seen in frozen sections in xanthoma, shew a different and very definite appearance—clear cut spherical globules, appearing as “Maltese crosses” under the crossed Nicol’s prisms.

This case clearly shews that saponification or hydrolysis of the fat may occur in sclerema neonatorum, although this saponification cannot be the primary event, since it has been absent from Harrison’s cases and the case described in this paper.

IV. NON-PANCREATIC FAT NECROSIS.

I have had the opportunity of examining one case, that of an adult male, in which saponification was found in the retroperitoneal fat. For this material I am indebted to Dr. H. A. Lucas.

An irregular mass arising from the retroperitoneal tissue was found incidentally at autopsy, in a man who died of arteriosclerosis of the coronary arteries; there was also a very large right inguinal hernia, but this had no relation to the mass in question, which was attached to the descending colon. There was no perforation of the gut, and it is improbable that the condition was due to an escape of pancreatic lipase. The mass was irregular in shape, and on macroscopic examination shewed fibrosis and small areas of calcification.

Paraffin sections. There is a broad band of formed fibrous tissue on the surface of the mass, and thick fibrous trabeculae running through it. There is no sign of recent inflammation.

The mass consists of fatty tissue, and there are groups of fat cells which contain a homogeneous hæmatoxylin-staining material; in some cases this “calcification” occupies the whole cell, but in most it occupies the periphery and forms a crescentic or annular mass.

Frozen sections. Unstained sections. Collections of short, rod-like crystals are present in some of the fat cells. Melting point, 35° – 42° C. The crystals are soluble in ether, petroleum ether, benzene, and alcohol. They probably consist of neutral fat.

In places there are rounded and gyrate hyaline masses, appearing milky under the crossed Nicol’s prisms. These masses are insoluble, even when heated, in ether and petroleum ether, and insoluble in 10% aqueous HCl. In acid alcohol (1% HCl in 95% alcohol), they are soluble at once in the cold. With acid alcohol (1% HCl in 60% alcohol), the immediate effect is to produce numbers of short, fine, anisotropic crystals, which dissolve when the section is warmed with the acid alcohol.

This suggests that these masses consist of soaps, which would yield fatty acids on treatment with acid alcohol, the fatty acids then dissolving in the alcohol.

Frozen sections stained by Benda’s solution, Sudan, and Hæmatoxylin. Some areas shew normal Sudan-stained fat containing a few crystals. Elsewhere there are very well-marked necrotic areas, in which are large, irregular masses consisting of the green, crystalline, doubly-refracting copper salt. In most of these masses the original form of the fat globules is lost; in places the original form is just recognisable by the annular or gyrate arrangement of the crystal masses, as if the contents of neighbouring cells had fused. Occasionally, in the midst of the copper soap, is seen a structureless material, deeply stained with hæmatoxylin,—possibly calcified material.

Around the green crystalline masses are fat cells which retain their structure. Some are filled with a homogeneous material, lightly stained with hæmatoxylin. Others still retain Sudan-stained fat, which usually does not fill them but forms globules or rings in the periphery of the cells.

Frozen sections stained by Benda’s solution, Hæmatoxylin, and Eosin. These shew the same features as above, but some cells are seen to be filled with an eosin-staining substance.

Benda’s reaction after treatment with alcohol. After removal of the free fatty acid by warming with 95% alcohol, the sections still give Benda’s reaction as strongly as before. The reaction, therefore, must be mainly due to soaps.

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Nile blue staining. The necrotic areas shew dark blue masses containing short crystals; these masses seem to correspond with the masses of copper crystals in the Benda-stained sections. Elsewhere in the necrotic areas are fat cells filled with a pale blue substance. These seem to correspond with the cells described above as containing material staining with eosin or hæmatoxylin. The normal areas contain pink-stained fat which contains crystals. If the section is heated, the crystals when melted merge with the surrounding material and take on the same colour as the surrounding material, blue or pink as the case may be.

It is difficult to interpret all the staining reactions here seen, but it is clear that the material shews a fat necrosis associated with saponification and calcification, and the appearance of the stained frozen sections is very similar to that described by Carol and Van der Zande in their case of "adiponecrosis subcutanea neonatorum."

SUMMARY AND CONCLUSIONS.

(a) A case of sclerema neonatorum is reported, with observations on the histology and chemistry of the subcutaneous fat. Acicular crystals are present in the subcutaneous tissue, with an abnormally high melting point. These are not fatty acid crystals, but probably neutral fats. There is no hydrolysis of the fat. Chemical observations on the fat extracted by ether confirm the facts of the raised melting point and absence of hydrolysis. The tissue has a raised calcium content in the absence of radiological and microscopic evidence of calcification.

(b) A consideration of the literature shews that hydrolysis may occur in sclerema, and this explains the fact that the acid values of the cases reported by Harrison were slightly high. Sclerema neonatorum is thus brought into line with cases of non-pancreatic fat necrosis, although it is clear that in sclerema (as possibly in non-pancreatic fat necrosis) saponification is not the primary lesion.

(c) A case of saponification in the retroperitoneal tissue is described for comparison.

I wish to express my thanks to Dr. G. A. Harrison. The work was undertaken at his suggestion and carried out in his laboratories, first at Great Ormond Street, and later at St. Bartholomew's Hospital, and I am indebted to him for suggestions and advice throughout.

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