Intrathoracic hibernoma

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Benign tumours morphologically resembling the brown fat of the human embryo or infant and the interscapular gland of hibernating animals were first recognized 60 years ago. The term 'hibernoma', as applied to a human neoplasm, may be objectionable, but it has become justified by usage.

In human embryos brown fat is found in the interscapular region, neck, and axillae; in the mediastinum and below the parietal pleura; in

the omental, periadrenal, and perinephric fat; in the groins and, as detached foci, in the peripheral parts of the limbs (Shaw, 1901; Rasmussen, 1923; Aherne and Hull, 1964). Microscopically it consists of lobules of round cells about half the size of fat cells, with a granular or foamy cytoplasm and a small round centrally placed nucleus (Fig. 1). The brown colour is apparently due to a high concentration of cytochromes (Joel and Ball, 1960).

FIG. 1. Brown fat surrounding adrenal pheochromocytoma (H. and E. $\times 100$).

The difference between brown fat and normal adipose tissue is not simply morphological. Both brown fat and hibernomata are more vascular, and, when analysed, they have certain chemical differences, notably a higher phospholipid content (Cox, 1954). Experimental animal studies have shown that brown fat has significant metabolic differences from ordinary fat and is under hormonal influences (Fawcett, 1952). Whether these properties extend to hibernoma in man is unknown. A curious but unexplained fact is the prominence of brown fat round pheochromocytoma in the human adult (Melicow, 1957; Fig. 1).

In an excellent survey of the literature Beetstra and Quast (1958) reviewed the 38 cases recorded up to 1958, four of which were intrathoracic. We have been able to trace 11 other cases and to add a twelfth, bringing the total up to 50 (Table I).

TABLE I
HIBERNOMATA REPORTED SINCE BEETSTRA AND QUAST (1958)

Author	Sex	Age	Situation
Putzmann (1957)	F	37	R. loin
May, D'Esopo, and Yesner (1960)	M	26	Intrathoracic
Gawlik and Czartoszewski (1960)	F	64	Interscapular
Sikorowa (1960)	M	29	Interscapular
Linares Pérez <i>et al.</i> (1963)	F	45	L. flank
Motta (1963)	M	40	Intra-abdominal
Pachaly, Schürmann, and Martínez (1964)	F	31	R. axilla
Pachaly <i>et al.</i> (1964)	F	35	Interscapular
Angervall, Nilsson, and Stener (1964)	M	40	R. femoral
Angervall <i>et al.</i> (1964)	F	27	R. femoral
Keshishian and Cox (1965)	F	41	Intrathoracic
Present case	M	54	Intrathoracic

As might be expected, the distribution of hibernoma approximates to that of brown fat, and of the 50 cases hitherto recorded 13 were interscapular, seven intrathoracic, seven axillary, seven femoral, three cervical, three in the abdominal parietes, two intra-abdominal, one popliteal, one intramammary, and six in unspecified situations.

CASE REPORT

R. C., an accountant aged 54, had suffered from asthma for 17 years. In 1958 he was found to be sensitive to mould spores, and following desensitization at the Wright-Fleming Institute he improved considerably. In 1959 a chest radiograph revealed a shadow on the right side, but this was not followed up. In 1963 his general practitioner referred him for mass miniradiography because of a chronic cough with white sputum, and a round shadow was observed in the central zone on the right side. By this time he

had developed a left inguinal hernia, and there was some history of pain in the right scapular region.

He was referred to Mr. Peter Jones at Westminster Hospital with a suspected lipoma of the chest wall, and a further radiograph was reported on by Dr. Basil Strickland as follows: 'There is a rounded opacity situated posteriorly in the right hemithorax (roughly 4 cm. in diameter) in the posterior axillary line. It is associated with a saucer-shaped "notch" on the inferior margin of the seventh rib. There are no differential densities within the mass, which presents the radiographic features normally associated with a neurofibroma or similar tumour' (Figs 2 to 4).

An intercostal neurofibroma was diagnosed and, as the lesion was readily accessible, thoracotomy was performed and a subpleural tumour was found lying against the seventh right rib. This shelled out easily. Convalescence was uneventful, and the patient remains well.

PATHOLOGY The tumour was rounded and encapsulated, 3.75 × 3.25 × 3 cm. in its diameters, and with a homogeneous brownish cut surface quite unlike ordinary fat (Fig. 5). Microscopically it consisted of three types of cell: (1) small granular, PAS-positive; (2) medium-sized vacuolated or multilocular, and sudanophile; (3) large unilocular fat cells. The tumour was more vascular than a lipoma and was divided into lobules by fine septa (Figs 6 and 7).

CHEMICAL ANALYSIS Half of the tumour was investigated by methods described elsewhere (Billimoria, Irani, and MacLagan, 1965a, b; Jepson, Billimoria, and MacLagan, 1965). For comparison, four benign lipomata were analysed using the same technique, and their mean composition was estimated (Table II). Data

TABLE II
LIPID FRACTIONS OF TISSUE

	Total Cholesterol		Phospholipid		Triglyceride	
	Total Lipid (%)	Weight (mg./100 g. wet wt.)	Total Lipid (%)	Weight (mg./100 g. wet wt.)	Total Lipid (%)	Weight (mg./100 g. wet wt.)
Hibernoma	0.4	150	3.6	1,300	96.0	34,960
Lipoma	0.2	118	0.7	332	99.1	48,150
Adipose tissue	0.3	—	0.1	—	99.6	—

on the composition of adipose tissue have been included for comparison (Hirsch, 1962). Although all the above tissues are mainly composed of triglycerides, the hibernoma was found to have an appreciably higher phospholipid content, 36 times greater than adipose tissue and five times greater than the lipoma.

The fatty acid composition of the three major classes of lipid in the hibernoma and lipoma is shown in Table III. The fatty acid values of the

FIG. 2

FIG. 2. *Radiograph of the chest showing the shadow of a tumour in the right hemithorax.*

FIG. 3. *Radiograph showing the tumour notching the 7th rib.*

FIG. 4. *Radiograph of the chest, lateral view.*

FIG. 3

FIG. 4

FIG. 5. *Naked-eye appearance of the tumour showing capsule and (right) cut surface.*

FIG. 6. *Photomicrograph of the tumour showing lobules of brown fat (H. and E. $\times 110$).*

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FIG. 7. Higher power photomicrograph showing granular, vacuolated, and unilocular cells (H. and E. $\times 550$).

TABLE III
MEAN FATTY ACID COMPOSITION OF THE TISSUE LIPIDS

Fatty Acid	Hibernoma			Lipoma			Adipose Tissue
	EC (%)	PL (%)	TG (%)	EC (%)	PL (%)	TG (%)	
12:0 ¹	3.0	2.5	1.5	1.0	2.0	Tr.	1.0
14:0	4.5	12.0	4.0	3.0	5.5	3.0	3.5
14:uns.	1.0	2.5	Tr.	1.0	2.0	1.5	Tr.
15:0	1.0	1.0	1.0	Tr.	Tr.	Tr.	Tr.
16:0	17.5	32.0	26.5	29.5	19.0	19.5	19.0
16:1	9.5	9.0	6.0	9.5	17.0	13.5	5.0
16:2	2.0	—	—	2.0	—	1.5	—
17:0	—	Tr.	—	Tr.	—	Tr.	Tr.
17:uns	—	—	—	Tr.	Tr.	Tr.	1.0
18:0	6.0	3.0	3.5	4.5	3.0	2.0	6.0
18:1	25.0	22.5	31.5	40.0	38.0	44.0	43.0
18:2	5.0	—	—	3.0	2.5	4.5	1.5
18:2	5.0	5.5	6.0	3.5	8.0	8.0	14.0
18:3	—	—	—	Tr.	—	—	Tr.
19:0	—	—	—	—	—	1.0	Tr.
20:0	6.5	3.0	—	Tr.	2.5	Tr.	1.0
20:1	—	—	—	Tr.	—	—	Tr.
20:2	—	—	—	—	—	—	—
20:3	14.5	Tr.	—	—	—	—	Tr.
20:4	—	—	—	—	—	—	—

uns.=unsaturated; Tr.=trace <0.5%; EC=ester cholesterol; PL=phospholipids; TG=triglycerides.
¹ The fatty acids are denoted by the number of carbon atoms before and the number of double bonds after the colon.

triglyceride fractions of adipose tissue are included for comparison.

The oleic acid (18:1) content of the hibernoma in all lipid fractions was much less than in adipose tissue or lipoma. In the ester cholesterol fraction this deficiency was made up mainly by increased levels of eicostrienoic (20:3), arachidic (20:0), and stearic (18:0) acids. In the phospholipid fraction the decreased oleic (18:1) and linoleic (18:2) acids were accompanied by an increase in palmitic acid (16:0).

The ester cholesterol fraction of the lipoma tissue showed very low levels of linoleic acid (18:2) and an increased palmitic acid (16:0). The phospholipid and triglyceride fractions showed increased palmitoleic acid (16:1) levels.

A fractionation of hibernoma phospholipids is shown in Table IV. In comparison with normal plasma phospholipids the levels of phosphatidyl-ethanolamine were very high, and some 26% of the total phospholipids was present as a lyso-phospholipid.

TABLE IV
PHOSPHOLIPIDS OF HIBERNOMA

	Hibernoma ¹	Plasma ¹
Phosphatidic acids	0.5	0.4
Phosphatidyl ethanolamine ..	23.0	8.0
Lysophosphatidyl ethanolamine ..	6.2	Trace
Lecithin + sphingomyelin ..	50.0	89.8
Lysolecithin	20.4	1.8

¹ Each fraction as a percent of total phospholipid

DISCUSSION

Of the 50 recorded cases of hibernoma, seven (including our own) have been intrathoracic. This is a relatively high incidence as compared with intrathoracic lipomata, since only 28 of the latter were recorded between 1933 and 1954 (Keeley and Vana, 1956), surely an infinitesimal fraction of the total number of lipomata of all sites excised during those years.

The intrathoracic hibernomata are summarized in Table V. Five patients were men, and in four the tumour was left-sided. Three patients were symptomless, and it is not certain that the chest symptoms in the remainder were due to the tumour. It is reasonable to suppose that with increasing mass-radiography intrathoracic hibernoma will be more frequently diagnosed. For this reason its close resemblance to intercostal neurofibroma, as observed by our colleague, Dr. Strickland, is an important point to note in the pre-operative diagnosis.

Since brown fat occurs in the mediastinum as well as outside the parietal pleura, it is curious that no case of mediastinal hibernoma has been reported hitherto. This represents a further difference from intrathoracic lipoma, which commonly involves the mediastinum, purely subpleural lipoma being rare (Keeley, Gumbiner, Guzauskus,

and Rooney, 1953; Ten Eyck, 1960). The hibernoma is also much smaller on average than the lipoma, the half a dozen cases recorded ranging from 3.5 by 3.1 by 1.4 cm. to 14 by 12 by 8 cm. Intrathoracic lipoma becomes symptomatic by virtue of its size and location, approximately half the recorded cases having had symptoms (Staub, Barker, and Langston, 1965).

A final difference is the consistently benign nature of the hibernoma, which, unlike the lipoma, seems to have no sarcomatous counterpart, unless we accept the dubious case of Apatenko and Poroshin (1962), which may well have been an undifferentiated liposarcoma. This is not to assert that a malignant hibernoma may not one day be recorded.

The chemical composition of the hibernoma appears to differ significantly from that of the lipoma or adipose tissue. The main findings show that the hibernoma has a much higher phospholipid content. This phospholipid fraction is rich in phosphatidylethanolamine and contains much higher quantities of lysophosphatides than are found in most other tissues. The fatty acid composition of the hibernoma indicates a higher state of saturation of the fatty acids, and consequently the fat appears to be less liquid than the lipoma or triglyceride. A remarkably high content of eicostrienoic acid was found in the ester cholesterol fraction of the hibernoma, which is not observed in other tissues. On the other hand, the lipoma tissue closely resembled adipose tissue.

SUMMARY

The total number of hibernomata recorded has been brought up to date and now amounts to 50, of which seven were intrathoracic.

TABLE V
INTRATHORACIC HIBERNOMA

No.	Author	Sex	Age	Chest Symptoms	Site of Tumour	Size of Tumour (cm.)	Weight of Tumour (g.)
1	Kittle <i>et al.</i> (1950)	F	42	Increasing cough and wheezing	Attached 3-6 L. ribs posteriorly	14 × 12 × 8	1,000
2	Gross and Wood (1953) (Case 1)	M	39	Pain L. upper chest and cough	Near L. apex with pedicle just above 1st rib	(a) 8 × 9 × 4 (b) 5 × 6 × 2	183
3	Peabody <i>et al.</i> (1953)	M	31	3 weeks' pleuritic pain in precordial area	Along lateral margin of 1st L. anterior rib space	3.5 × 3 × 1.4	?
4	Beetstra and Quast (1958)	M	22	Nil	R. dome with pedicle between large vessels and brachial plexus	5.5 × 5 × 2	?
5	May <i>et al.</i> (1960)	M	26	Nil	Periphery of L. hemithorax	4 (diameter)	?
6	Keshishian and Cox (1965)	F	41	Nil	R. posterior apical	4 (diameter)	?
7	Present case	M	54	Asthma, chronic cough, pain in R. scapular region	R. posterior axillary line, 6th rib space	3.75 × 3.25 × 3	?

A case is presented, and the intrathoracic tumours are briefly reviewed.

Hibernomata have a distribution, size, morphology, and chemical composition which differ significantly from those of lipoma and adipose tissue.

A full lipid analysis of the hibernoma in this case revealed a much higher phospholipid content and a generally higher saturated fatty acid composition of the other lipid fractions in comparison with the lipoma or adipose tissue.

Intrathoracic hibernoma may simulate intercostal neurofibroma radiologically.

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REFERENCES

- Aherne, W., and Hull, D. (1964). The site of heat production in the newborn infant. *Proc. roy. Soc. Med.*, **57**, 1172.
- Angervall, L., Nilsson, L., and Stener, B. (1964). Microangiographic and histological studies in 2 cases of hibernoma. *Cancer*, **17**, 685.
- Apatenko, A. K., and Poroshin, K. K. (1962). O morfologii i gistogeneze gibernomi. (On the morphology and histogenesis of hibernoma.) *Arkh. Pat.*, **24**, No. 2, p. 60.
- Beetstra, A., and Quast, W. H. A. (1958). Intrathoracic hibernoma. *Arch. Chir. Neerl.*, **10**, 203.
- Billimoria, J. D., Irani, V. J., and MacLagan, N. F. (1965a). Phospholipid fractionation and blood clotting. *J. Atheroscler. Res.*, **5**, 90.
- (1965b). Blood lipid fractionation and blood clotting in ischaemic heart disease. *Ibid.*, **5**, 102.
- Cox, R. W. (1954). Hibernoma: the lipoma of immature adipose tissue. *J. Path. Bact.*, **68**, 511.
- Fawcett, D. W. (1952). A comparison of the histological organization and cytochemical reactions of brown and white adipose tissues. *J. Morph.*, **90**, 363.
- Gawlik, Z., and Czartoszewski, A. (1960). Przypadek brunatnego tłuszczaka. (A case of brown lipoma.) *Pat. pol.*, **11**, 195.
- Gross, S., and Wood, C. (1953). Hibernoma. *Cancer*, **6**, 159.
- Hirsch, J. (1962). Composition of adipose tissue. In *Adipose Tissue as an Organ. Proceedings of the Duell Conference on Lipids*, p. 83. Ed. L. W. Kinsell, Thomas, Springfield, Illinois.
- Jepson, E. M., Billimoria, J. D., and MacLagan, N. F. (1965). Serum and tissue lipids in patients with familial xanthomatosis. *Clin. Sci.*, **29**, 383.
- Joel, C. D., and Ball, E. G. (1960). Electron transmitter system in adipose tissue. *Fed. Proc.*, **19**, 32.
- Keeley, J. L., Gumbiner, S. H., Guzauskus, A. C., and Rooney, J. A. (1953). Mediastinal lipoma: the successful removal of 1,700 gram mass. *J. thorac. Surg.*, **25**, 316.
- and Vana, A. J. (1956). Collective reviews. Lipomas of the mediastinum, 1940 to 1955. *Int. Abstr. Surg.*, **103**, 313.
- Keshishian, J. M., and Cox, P. A. (1965). Intrathoracic hibernoma. Report of a case. *Dis. Chest*, **47**, 348.
- Kittle, C. F., Boley, J. O., and Schafer, P. W. (1950). Resection of an intrathoracic hibernoma. *J. thorac. Surg.*, **19**, 830.
- Linares Pérez, M., Oliva Aldamiz, H., Navarro Berástegui, V., and Valle Jimenez, A. (1963). Un tumor humano poco común: el hibernoma. Estudio de un caso. *Rev. clin. esp.*, **81**, 372.
- May, C. J., D'Esopo, N. D., and Yesner, R. (1960). Intrathoracic hibernoma. *Amer. Rev. resp. Dis.*, **82**, 555.
- Melicow, M. M. (1957). Hibernating fat and pheochromocytoma. *Arch. Path.*, **63**, 367.
- Motta, R. (1963). Un caso di hibernoma. *Minerva chir.*, **18**, 28.
- Pachaly, L., Schürmann, R., and Martinez, A. (1964). Bericht über zwei sog. Hibernome, Tumoren des braunen Fettgewebes. *Zbl. allg. Path. path. Anat.*, **105**, 370.
- Peabody, J. W., Ziskind, J., Buechner, H. A., and Anderson, A. E. (1953). Intrathoracic hibernoma: third reported case. *New Engl. J. Med.*, **249**, 329.
- Putzmann, G. (1957). Über ein braunes Lipom. *Zbl. allg. Path. path. Anat.*, **96**, 25.
- Rasmussen, A. T. (1923). The so-called hibernating gland. *J. Morph.*, **38**, 147.
- Shaw, H. B. (1901). A contribution to the study of the morphology of adipose tissue. *J. Anat. (Lond.)*, **36**, 1.
- Sikorowa, H. (1960). Quoted by Gawlik and Czartoszewski (1960).
- Staub, E. W., Barker, W. L., and Langston, H. T. (1965). Intrathoracic fatty tumors. *Dis. Chest*, **47**, 308.
- Tent Eyck, E. A. (1960). Subpleural lipoma. *Radiology*, **74**, 295.