Histiocytosis X

By J. B. Booth and R. S. A. Thomas (London)

A case is presented, of a two year-old child, in whom Histiocytosis X occurred as an isolated lesion in the larynx, and was completely controlled one year after treatment. No previous similar case has been described though several cases showing granulomatous change, either as deep ulcers or multiple grey/yellow tumours in the larynx, trachea and bronchi have been recorded. The initial diagnosis was difficult due to the technical problem of obtaining a satisfactory biopsy from beneath the vocal cords, which had become firmly bound together. Recent advances in electron microscopy have shown inclusion bodies in the histiocytes of this condition, which seem to offer a further diagnostic aid. The treatment of these cases with steroid therapy is often successful and was given empirically in this case but without benefit. A course of radiotherapy resulted in regression of the tumour. Surgery or cytotoxic drugs would have been other possible alternatives but were considered unsuitable as the initial treatment in so young a patient.

Case report

A.H., a male infant aged two years, from Dubai in the Persian Gulf, was admitted to the American University Hospital in Beirut, Lebanon, on 21 July 1968, with progressively increasing dyspnoea for three weeks. There was no previous history of cough, fever or foreign body aspiration, nor of similar trouble in the past. During the two days prior to admission he had become febrile and had developed a whoop-like cough.

Examination on admission showed a child (height 83 cm. weight 10·3 kg.) with severe retraction of the chest wall and suprasternal notch and mild cyanosis; respiration rate—40 per minute. The remainder of the examination was normal. Investigation of the blood (haemoglobin, WBC, ESR, serum calcium, magnesium, iron, TIBC and serum proteins) and urine showed no significant abnormality; radiography showed some laryngeal narrowing.

The patient's condition necessitated an immediate laryngoscopy and tracheostomy; at operation diffuse subglottic oedema was seen. Swabs of the laryngeal secretions revealed no pathogenic organisms. The child was given ampicillin and prednisone post-operatively with improvement in the chest condition, but subsequent attempts at decannulation were unsuccessful.

On the seventeenth day of admission (6 August), a repeat direct laryngoscopy was carried out; the subglottic oedema was still present and in addition a small subglottic mass was noted on the right side. Tissue was taken for histological examination which revealed a squamous epithelial surface with an under-

https://doi.org/10.1017/S002221510015652X Published online by Cambridge University Press

lying fibrous stroma heavily infiltrated by cells, the majority of which were histiocytes, and reticulum cells with large vesicular nuclei. Three days later, on 9 August, some more tissue was removed. Examination now showed foci of chronic inflammation with fibroblastic activity and histiocytic infiltration, the latter showing some pleomorphism and much phagocytic activity, the overlying epithelium was involved to a variable degree by an acute inflammatory reaction (Fig. 1).

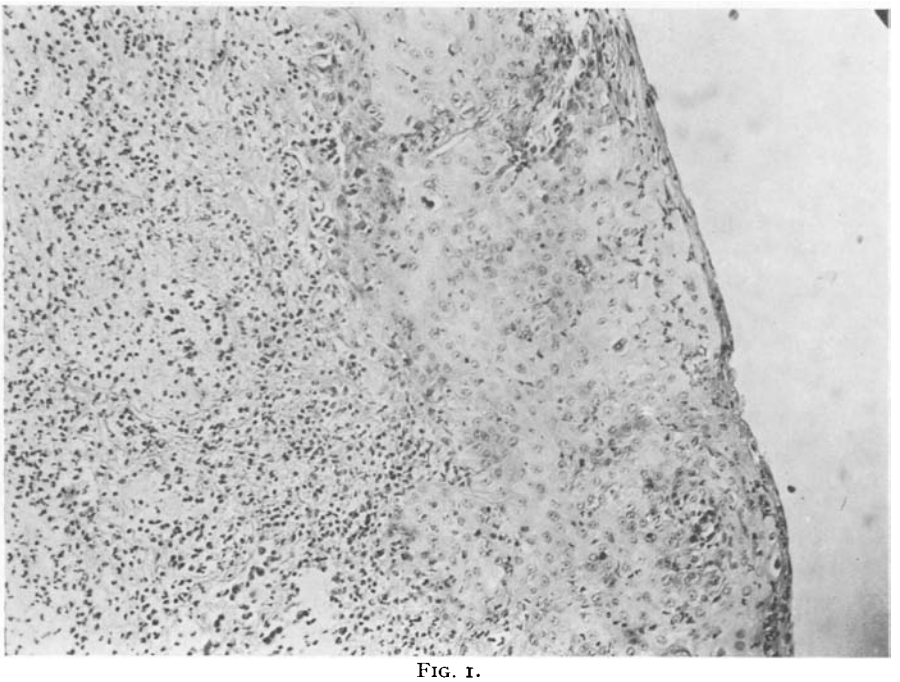


FIG. 1.
Biopsy (9.8.68.) × 100, showing histiocytic infiltration.

On 18 August, the patient was transferred to this hospital. The following day, a direct laryngoscopy was carried out; the vocal cords could not be seen to abduct and blood oozed from their surfaces. A nodular mass was seen on the posterior half of the left cord with the appearance of granulation tissue. Bronchoscopy through the tracheostomy opening did not reveal any abnormality. A week later a repeat laryngoscopy was undertaken. The cords had the same appearance as previously; no opening could be seen between them nor could one be defined by gentle bouginage. On 30 August, under general anaesthesia, polytomograms of the larynx were taken (Fig. 2) demonstrating that the subglottic space was occluded superiorly by a sharply demarcated soft tissue mass. The larynx was not aerated and appeared to have been completely obliterated by the mass. Further tissue was therefore required to make an histological diagnosis. At laryngoscopy (3 September 1968) the appearance of the cords was unchanged, but they were separated with difficulty and a 'blind' biopsy taken from the subglottic mass. Unfortunately insufficient material

https://doi.org/10.1017/S002221510015652X Published online by Cambridge University Press

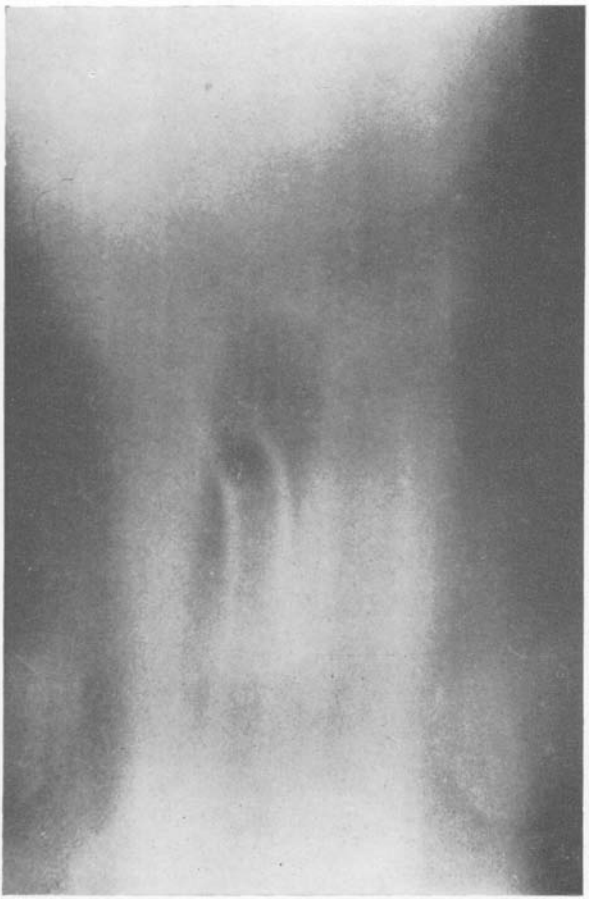


FIG. 2.
Tomogram of Larynx (30.8.68.).

could be obtained for electron microscopic studies. The tissue consisted of densely packed histiocytes in some fibrous stroma and a few eosinophils; some of the histiocytes were multi-nuclear (Figs. 3, 4, 5). A diagnosis of histiocytosis X was made. A radiographic skeletal survey, including the skull, showed no abnormality. On 16 September, the patient was transferred to the Hammersmith Hospital for radiotherapy. He received a total of 1,400 r. in 3 divided doses at weekly intervals through 5 × 4 cm. directly opposed fields from an 8 million volt linear accelerator. On return to this hospital, a repeat direct laryngoscopy was carried out (7 October), which showed the left vocal cord to be elongated and folded over anteriorly; the right cord appeared shortened and pushed up by a mass inferiorly. The cords could now be separated but still only with difficulty. A further biopsy was taken which showed the same features as that taken a month previously. A week later the patient was discharged home with no improvement in his clinical condition. Prior to his admission

https://doi.org/10.1017/S002221510015652X Published online by Cambridge University Press

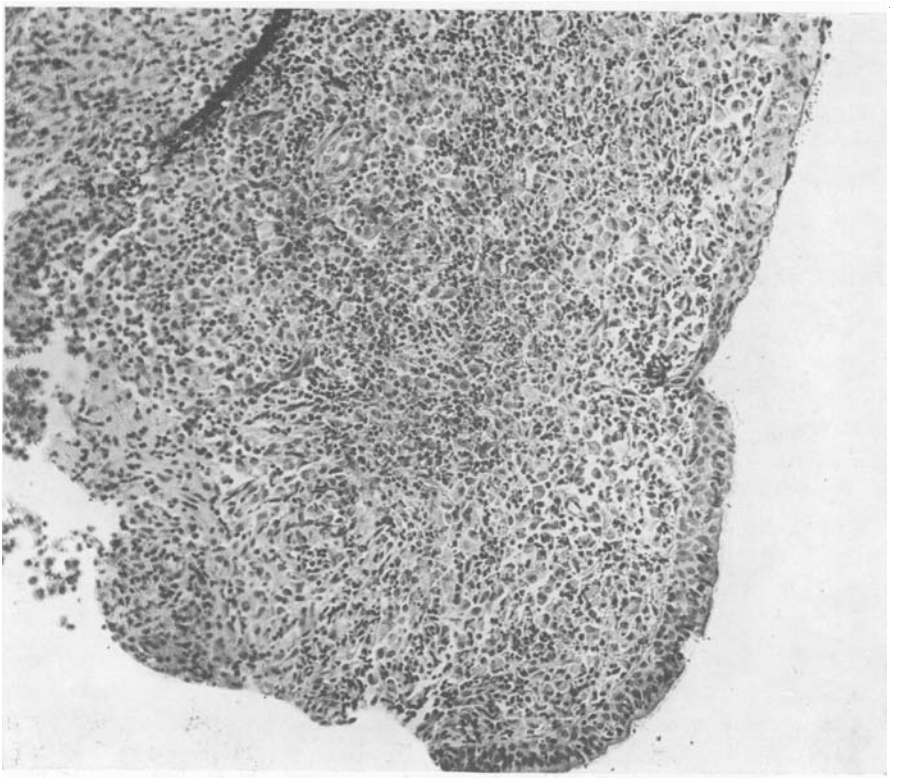


FIG. 3.
Biopsy (3.9.68.) × 150, showing densely packed histiocytes and a few eosinophils.

here, the child had been on prednisone 5 mg. daily; he was therefore given operative cover with a total dosage of hydrocortisone 150 mg., cortisone 300 mg., prednisone 60 mg.

On 20 January 1969, the child was re-admitted, symptom-free and talking. A follow-up direct laryngoscopy was carried out the following day. The right vocal cord was noted to be sluggish in its movement compared with the left, which was now normal. There was also a slight irregularity of the edge of the right cord but no evidence of tumour. A small web was noted in the anterior part of the subglottic area. Post-operatively the patient was successfully decannulated and he was discharged home again a week later. A recent communication from the father (December 1969) confirms that the child's condition continues to remain satisfactory.

Discussion

The suggestion that Hand-Schüller-Christian Disease, Letterer-Siwe Disease and Eosinophilic Granuloma might be different forms of the same condition was first put forward by Wallgren (1940), and Farber (1941). It is interesting to note that Lichtenstein, Jaffe and Otani were present when

https://doi.org/10.1017/S002221510015652X Published online by Cambridge University Press

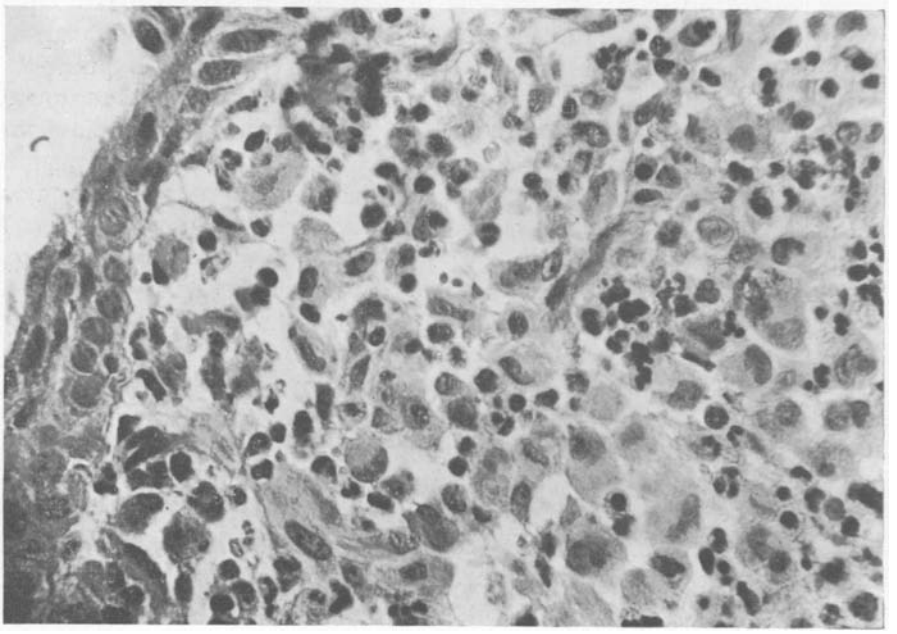


FIG. 4.
Same specimen × 700.

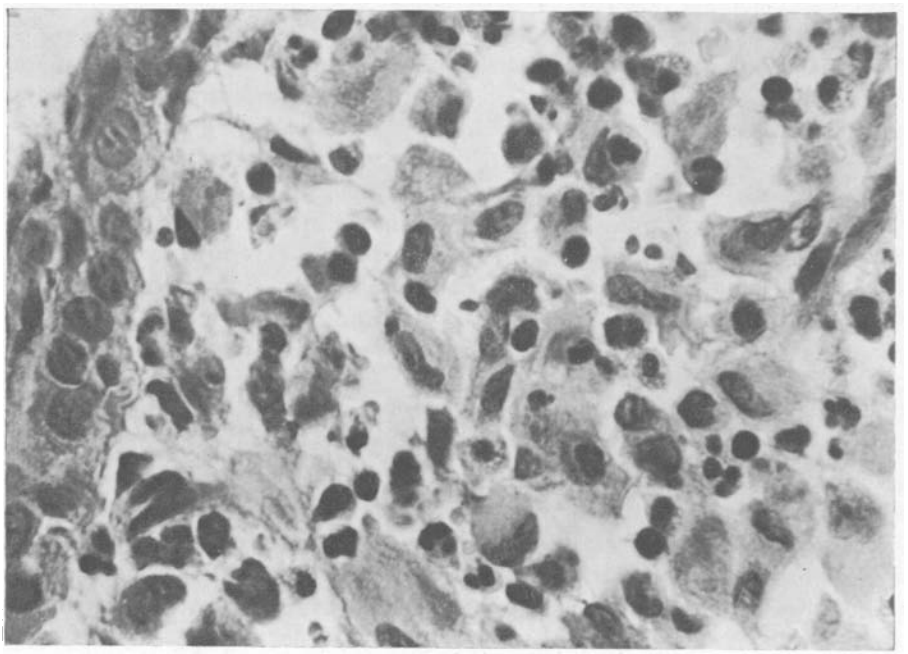


FIG. 5.
Same specimen × 1150.

https://doi.org/10.1017/S002221510015652X Published online by Cambridge University Press

Farber presented his case and at that time all disagreed with the idea. Later Lichtenstein (1953), was to suggest that all three conditions represented a single integrated entity for which he proposed the name—histiocytosis X. More recently he has reappraised the various facets and modes of presentation of these three types of the same disease (Lichtenstein, 1964). Eosinophilic granuloma of bone is regarded as localized histiocytosis X. The acute (or subacute) disseminated form was formerly labelled Letterer-Siwe Disease, and chronic disseminated histiocytosis X represents Schüller-Christian Disease. In a review of forty cases, Oberman (1961), analyzed them under three similar titles: Group 1—disease confined to bone at onset (eosinophilic granuloma). Group 2—skeletal and visceral or soft tissue lesions present at onset (Hand-Schüller-Christian Disease). Group 3—disease confined to skin, soft tissues or viscera at onset (Letterer-Siwe Disease). The concept of a unified disease entity has been strengthened recently by the finding of intra-cytoplasmic structures in the abnormal histiocytes of all three conditions thus suggesting a single aetiology.

Hand-Schüller-Christian Disease is the variant most commonly seen in the child and young adult, though no age group is exempt. It is classically stated to consist of a triad of multiple defects of the cranial bones, exophthalmos and diabetes insipidus, though probably not more than 10 per cent of cases have all three. The presence of skeletal lesions is no longer considered essential for the diagnosis though they may appear long after those in extraskeletal sites. Diabetes insipidus may be found without apparent skull lesions. The lesions causing the latter are said to occur in any or all of three centres, the posterior lobe of the pituitary gland, the tuber cinereum and the pathways around the third ventricle. The exophthalmos is bilateral and is caused either by granulomata in the orbits or in the orbital plate of the frontal bone. The chronic disseminated form of histiocytosis X may present as eosinophilic granuloma in the skin, mouth, vulva, lymph nodes, liver, kidney and lung (Winkelmann, 1969). Cases with co-existing lesions in the lung carry a more serious prognosis than those with isolated involvement (Melhem *et al.*, 1964).

Typically Letterer-Siwe Disease runs a rapidly progressive course characterized by fever, skin rash, rapidly progressive anaemia and purpura, and usually occurs under the age of two years; cases causing stillbirth have also been reported.

Eosinophilic granuloma was originally described by Finzi (1929), and later, but quite independently, in 1940, by Otani and Ehrlich, and Lichtenstein and Jaffe, as tumour-like destructive swellings of bone, usually solitary but occasionally multiple. The lesions occur in the skull (including ear, nose and sinuses), ribs, spine, pelvis, scapula, clavicle, and long bones but almost never in the hands and feet (Mallory, 1942; Tos, 1966).

https://doi.org/10.1017/S002221510015652X Published online by Cambridge University Press

Histiocytosis X

This variant usually affects older children and adults but can also be seen in infants and in the elderly. The lesions are usually osteolytic and circumscribed, but diffuse or sclerotic lesions have been seen (Ochsner, 1966). In histiocytosis X, the histiocytes are seen in a variety of pathological forms but there is no longer any suggestion of any variant being a so-called 'storage disease'. Four phases have been described in the formation of an eosinophilic granuloma, but they frequently merge into each other. In the earlier stages the disease is characterized by the proliferation of histiocytes and the accumulation of eosinophils, but later by the formation of the xanthoma cell. The alternative descriptive title of 'eosinophilic xanthomatous granuloma' has been proposed (Thannhauser, 1958; Bolande, 1967). In each type, the younger the individual is affected, the more rapid and destructive is the course of the disease.

Manifestation in the larynx. A search for cases similar to the one reported here revealed several which have been labelled 'reticulo-histiocytoma' but on closer scrutiny are reticulosarcoma or primitive lymphosarcoma (Madonia and Catalano, 1955; Di Girolamo, 1962; Ferreri and Liberti, 1956; Laudadio and Puxeddu, 1966). Reticulo-histiocytoma occuring in the skin is however well authenticated, but no cases showing similar pathology have been seen in the larynx. Other cases have been described which might more correctly be labelled angioma or eosinophilic cystadenoma (Mordret and Paller, 1953; Bonet, 1960). Xanthomata of the larynx have been reported and they are seen as non-ulcerated, slightly lobulated masses which are yellow in colour. They may involve any or all parts of the mouth, pharynx and larynx (xanthoma disseminata) or rarely they may occur in the larynx alone. Such involvement may cause considerable distortion of the upper respiratory tract and this has occasionally necessitated tracheostomy or surgical removal. Xanthoma disseminata is usually associated with skin lesions and it should be noted that diabetes insipidus may also be present (Turner *et al.*, 1925; Finney *et al.*, 1932; New, 1935; Montgomery and Osterburg, 1938). Granulomatous changes in the larynx causing deep ulceration of the mucosa have also been described (Müller, 1938). Three cases are of further interest: first a patient with eosinophilic granuloma of the frontal bone and in addition a carcinoma of the larynx (Morselli and Perucci, 1962). Second, a patient with eosinophilic granuloma of the mastoid bone later developed a swelling of the right side of the neck and a husky voice but the larynx was not observed (Dawes, 1954, Case 2). Third, a case which showed lesions in the skin, tonsil, vallecula, soft palate, tongue, floor of the nose and conjunctiva which were originally thought to be Hodgkin's disease was ultimately considered to be eosinophilic granuloma (Brunner, 1951).

Investigations

When a diagnosis of histiocytosis X is being considered, a full skeletal

https://doi.org/10.1017/S002221510015652X Published online by Cambridge University Press

radiographic survey including skull is necessary. A biopsy of the lesion, if obtainable, must be included and if this is from the lung several are recommended. Biochemical tests have not proved helpful and the serum cholesterol is never elevated. Examination of a blood film frequently shows a moderate leucocytosis with a relative neutrophilia; a mild eosinophilia (3–10 per cent) may also be present but higher values are unusual. The erythrocyte sedimentation rate is usually within normal limits or only slightly elevated. Tests to exclude diabetes insipidus are necessary. Bacteriological, viral and fungal studies have always been found to be negative. However, sputum from cases with pulmonary involvement may show large numbers of eosinophils or fat-laden histiocytes (Lewis, 1964). Recently electron-microscopic studies have shown rod-like tubular structures in the cytoplasm of the histiocytes in histiocytosis X. The structures appear to have a constant form and invariably contain a central filament; they have never been found inside the nucleus or outside the histiocyte. Normal histiocytes do not possess these particles and it has been suggested that they may be viral in origin. Similar particles have been found in Langerhan's epidermal cells and so far the relationship between them remains unexplained (Basset *et al.*, 1966; Turiaf and Basset, 1967; De Man, 1968).

Treatment

Four types of treatment are available, either singly or in combination, in histiocytosis X: surgery, radiotherapy, steroids, and cytotoxic chemotherapy. Localized lesions in bone are best treated either by curettage or by radiotherapy but neither of these is practicable in the disseminated form. Where steroids in high dosage remain the treatment of first choice a dose of 2–4 mg. per kg. body weight is advised; a lack of response to one type does not preclude a trial of others with possible subsequent benefit. (Levin, 1955; Avioli *et al.*, 1963). However, in cases with mild pulmonary involvement it may be possible to withhold treatment reserving it for more rapidly progressive episodes. Nevertheless the view is held by some that to get clearing of the lungs radiographically, steroids must always be given for a period. What is certain, however, is that they should be given at a time when the disease is potentially reversible. Steroids are also to be preferred in children with localized lesions in bone situated near the epiphysis, where irradiation might interfere with future growth. The side effects of steroids may require that they be discontinued for short periods and in order to maintain treatment, folic acid antagonists have been given during such periods with advantage (Mermann and Dargeon, 1955; Freud, 1961). In the acute form of the condition, steroids combined with selective antibiotic therapy in high dosage offer the best form of treatment.

Cytotoxic agents such as cyclophosphamide, uracil mustard and thio-

https://doi.org/10.1017/S002221510015652X Published online by Cambridge University Press

Tepa etc. have been used without effect on the disease but vinblastin sulphate in doses of 0·1 – 0·5 mg. per kg. body weight has been successful in refractory cases. The drug is given at weekly intervals starting at the lower dosage and increased by 0·05 mg. per kg. increments until the higher dose is reached. Steroids may also be given concurrently (Beier *et al.*, 1963; Sharp *et al.*, 1964; Siegel and Coltman, 1966).

Summary

A two year old child from Dubai in the Persian Gulf presented with rapidly progressive dyspnoea which necessitated emergency tracheostomy. Subsequent investigations confirmed a subglottic soft-tissue mass arising chiefly from the right side, which on histology was shown to be histiocytosis X. No other evidence of the condition could be found in bone, lung or elsewhere in the body. Initial treatment with steroids produced no improvement but radiotherapy gave an apparently satisfactory result.

This is believed to be the first case reported in the larynx either as an isolated lesion or as part of the disseminated form of the condition.

Acknowledgements

We would like to thank Mr. Maxwell Ellis under whose care the patient was admitted, for allowing us to record the case and for his help in the preparation of the manuscript. The radiotherapy was carried out under Dr. Robert Morrison at the Hammersmith Hospital. We should also like to thank Professor I. Friedmann and Dr. D. A. Osborne, Department of Pathology, Professor A. E. Claireaux, The Hospital for Sick Children, and Professor C. E. Stroud, King's College Hospital Medical School for their help and advice. We are indebted to Mr. D. Connolly, Department of Clinical Photography for the illustrations. We are grateful to Dr. Nassif under whose care the patient was admitted to the American University Hospital, Beirut, and to Dr. L. Ghandur-Mnaymneh and Dr. A. Nasr for allowing us to use their material (Fig. 1).

REFERENCES

Avioli, L. V., Lasersohn, J. T., and Lopresti, J. M. (1963) *Medicine (Baltimore)*, **42,** 119.

Basset, F., Nézelof, C., and Turiaf, J. (1966) *Bulletins et mémoires de la Société de médicine de Paris*, **117,** 413.

Beier, F. R., Thatcher, L. G., and Lahey, M. E. (1963) *Journal of Pediatrics*, **63,** 1087.

Bolande, R. P. (1967) *Cellular aspects of developmental pathology*. London, p. 133.

Bonet, G. (1960) *Acta oto-rino-laringólica Ibéro-Americana (Barcelona)*, **11,** 81.

Brunner, H. (1951) *Oral Surgery, Oral Medicine and Oral Pathology*, **4,** 623.

Dawes, J. D. K. (1954) *Journal of Laryngology and Otology*, **68,** 575.

De Man, J. C. H. (1968) *Journal of Pathology and Bacteriology*, **95,** 123.

Di Girolamo, A. (1962) *Il Valsalva*, **38,** 301.

https://doi.org/10.1017/S002221510015652X Published online by Cambridge University Press

FARBER, S. (1941) *American Journal of Pathology*, **17,** 625.
FERRERI, G., and LIBERTI, R. (1956) *Il Valsalva*, **32,** 148.
FINNEY, W. P., MONTGOMERY, H., and NEW, G. B. (1932) *Journal of the American Medical Association*, **99,** 1071.
FINZI, O. (1929) *Minerva medica, Roma*, **9,** 239.
FREUD, P. (1961) *Journal of the American Medical Association*, **175,** 82.
LAUDADIO, P., and PUXEDDU, P. (1966) *Oto-rino-laryngologia, Italiana, Bologna*, **35,** 328.
LEVIN, H. (1955) *Journal of Pediatrics*, **46,** 531.
LEWIS, J. G. (1964) *Quarterly Journal of Medicine*, **33,** (n.s.) 337.
LICHTENSTEIN, L. (1953) *Archives of Pathology*, **56,** 84.
—— (1964) *Journal of Bone and Joint Surgery*, **46(A),** 76.
——, and JAFFE, H. L. (1940) *American Journal of Pathology*, **16,** 595.
MADONIA, T., and CATALANO, G. B. (1955) *Clinica oto-rino-laringo-iatrica, Roma*, **7,** 259.
MALLORY, T. B. (1942) *New England Journal of Medicine*, **227,** 955.
MELHEM, R. E., HAJJAR, J-J., and BALASSANIAN, N. (1964) *British Journal of Radiology*, **37,** 898.
MERMANN, A. C., and DARGEON, H. W. (1955) *Cancer*, **8,** 112.
MONTGOMERY, H., and OSTERBURG, A. E. (1938) *Archives of Dermatology and Syphilology*, **37,** 373.
MORDRET, J., and PALLER, R. (1953) *Annales d'oto-laryngologie, Paris*, **70,** 160.
MORSELLI, L., and PERUCCI, U. (1962) *Il Valsalva*, **38,** 194.
MÜLLER, H. (1938) *Zeitschrift für Kinderheilkunde*, **59,** 476.
NEW, G. B. (1935) *Archives of Otolaryngology*, **22,** 449.
OBERMAN, H. A. (1961) *Pediatrics*, **28,** 307.
OCHSNER, S. F. (1966) *American Journal of Roentgenology* **97,** 719.
OTANI, S., and EHRLICH, J. C. (1940) *American Journal of Pathology*, **16,** 479.
SHARP, H., WHITE, J. G., and KRIVIT, W. (1964) *Cancer Chemotherapy Reports*, **39,** 53.
SIEGEL, J. S., and COLTMAN, C. A. (1966) *Journal of the American Medical Association*, **197,** 403.
THANNHAUSER, S. J. (1958) *Lipidoses: diseases of the intra-cellular lipoid metabolism.* 3rd. Edn. New York. p. 345.
TOS, M. (1966) *Acta oto-laryngologica*, **62,** 217.
TURIAF, J., and BASSET, F. (1967) *Minerva medica, Roma*, **58,** 1074.
TURNER, A. L., DAVIDSON, J., and WHITE, A. C. (1925) *Edinburgh Medical Journal*, **32,** 153.
WALLGREN, A. (1940) *American Journal of Diseases of Children*, **60,** 471.
WINKELMANN, R. K. (1969) *Proceedings of the Staff Meetings of the Mayo Clinic*, **44,** 535.

The Royal National Throat, Nose and Ear Hospital,
and Institute of Laryngology and Otology,
Gray's Inn Road,
London, W.C.1.

https://doi.org/10.1017/S002221510015652X Published online by Cambridge University Press