

Sarcoid-like disorder of the intracranial optic nerve

Clinicopathological report of two cases

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SUMMARY Two cases with a sarcoid-like disorder apparently restricted to the intracranial optic nerve and the adjacent dura mater are described, doubling the number of reported cases. In both instances there were unilateral visual loss and unusual radiographic changes in the optic canal area. Biopsy samples showed localised infiltration of tissues with non-caseating tubercles containing epithelioid and multinucleated giant cells.

Sarcoidosis confined to the intracranial portion of the optic nerve and its vicinity is a distinct rarity which presents great diagnostic problems. We have found only two well-documented cases in the earlier literature. We report here our experiences from two other cases with an apparently solitary sarcoid-like affection of the optic canal area. Both patients had unilateral visual loss and unusual radiographic changes, superficially reminiscent of sphenoidal meningioma.

Case reports

CASE 1

A 70 year old former cab driver underwent surgery for a gastric ulcer at the age of 45 years, and had a thoracotomy with removal of circumscribed emphysema at the age of 69 years. His general health was otherwise good. At the age of 70 years he began to suffer from right orbital and peri-orbital pains. Examination at his county hospital disclosed a raised ESR (137 mm in 1 hour), and slight iron-deficiency anaemia. Pulmonary radiographs showed apparently inactive apex lesions but were otherwise normal. A skull series revealed a cystic area in the medial part of the right minor sphenoid wing, interpreted as a probable air sinus anomaly. Bilateral temporal artery biopsy samples were normal, as was an eye examination. Oral prednisolone had no striking effect on the orbital pains, but the ESR dropped to 60 mm per hour during the next two months. After a few days of evanescent diplopia, the

patient suffered several attacks of severe orbital and peri-orbital pains on the right. He was then referred to the University of Göteborg for further evaluation.

Neurological and neuro-ophthalmological examinations disclosed no abnormality except for impaired supra-orbital and corneal sensitivity on the right, and a Horner's syndrome on the same side. A diagnosis of Raeder's paratrigeminal syndrome was made, and neuroradiological studies for a probable right cavernous sinus lesion were recommended. A few days later, the patient awoke in the morning with visual loss on the right. Acuity had dropped from 1.0 to 0.2, and a dense central scotoma was found on perimetry. There was a corresponding afferent pupillary defect, but no fundus abnormality was seen. The visual loss was thought to depend on optic nerve infarction or bleeding within a sphenoidal meningioma.

Further skull films showed an unchanged cystic area in the right ala minor, where bone thickness was increased (Fig. 1). Hypocycloidal tomograms of the optic canal were normal. A right internal carotid angiogram was within normal limits. Selective external carotid angiograms showed some widening and tortuosity of a branch of the middle meningeal artery, and a very faint 'blush' in the region of the sphenoid wing cyst. Orbital venography proved that the superior orbital vein was occluded at the level of the superior orbital fissure. Pneumoencephalography was non-contributory. Isotopic brain scan disclosed a faint uptake corresponding to the superior orbital fissure.

On craniotomy the dura mater covering the right posterior orbital roof was found to be

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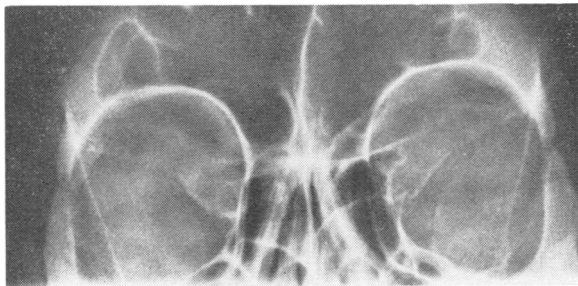


Fig. 1 Case 1. Increased thickness of ala minor on right, with cystic sclerosis in medial part. Frontal view.

irregularly thickened, with increased vascularisation. Meningioma-like tissue filled the cystic area seen on radiographs of the sphenoid wing. The optic nerve was grossly normal, although the dural abnormality extended into the roof of the optic canal. All areas of macroscopic dural abnormality were removed.

Microscopic examination of the extirpated dura mater showed thickening with an infiltration of inflammatory cells, chiefly lymphocytes and plasma cells. There was some focal fibrinoid necrosis, occasionally with an associated neutrophil leucocyte infiltration. In some regions there were tubercle formations, with central pale epithelioid cells and multinucleated giant cells (Fig. 2). Small vessels were frequently thick-walled. In a few bone fragments the marrow was fibrotic and infiltrated with chronic inflammatory cells. There was similar infiltration in a fragment of respiratory mucous membrane. There was neither caseous necrosis nor acid-fast bacilli. A diagnosis of granulomatous inflammation consistent with sarcoidosis was made.

After surgery, the patient exhibited a complete ocular motor paralysis on the right, presumably related to diathermy of the tissues in the superior orbital fissure. The orbital pains disappeared but there was no improvement in vision. During the

subsequent months vision was successively lost in the right eye, and the right optic disc turned pale. The ophthalmoplegia did not resolve.

A diligent search for evidence of multisystem sarcoidosis was largely negative. There was a raised CSF protein level (8.4 and 9.0 g/l), with electrophoretic evidence of blood-brain barrier damage and immunopathy. Alpha and, especially, gamma globulins were increased in the serum. CSF cellular analysis disclosed mesenchymal-histiocytic cells and lymphocytes of varying maturity. A quadriceps muscle biopsy was normal. There was no hypercalcaemia. Immunological testing disclosed a relative cutaneous anergy to various antigens, including candida, Varidase, tuberculin and dinitrochlorobenzene. The Kveim test was not available.

Treatment with oral prednisolone was continued. There were no clinical changes during the following year.

CASE 2

This 45 year old truck driver suddenly noticed visual loss in the left eye. Except for some pain centred on the left eye, he had no other symptoms. Ophthalmological examination at his local hospital confirmed a drop in visual acuity from 1.0 to 0.2 on the left, and a lower visual field defect in

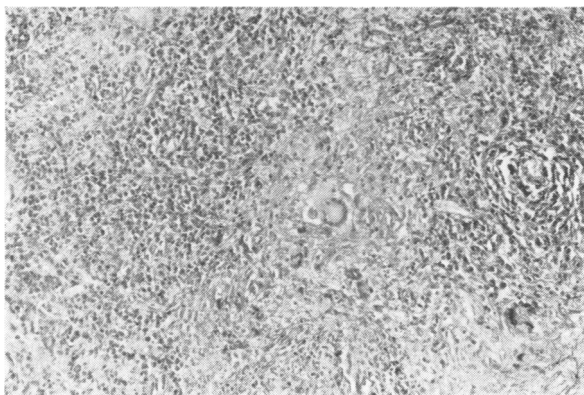


Fig. 2 Case 1. Microscopic picture of dural biopsy specimen. Diffuse infiltration of lymphocytes and plasma cells is punctuated by small collections of epithelioid and multinucleated giant cells, and by foci of fibrinoid necrosis. Haematoxylin van Gieson, $\times 380$

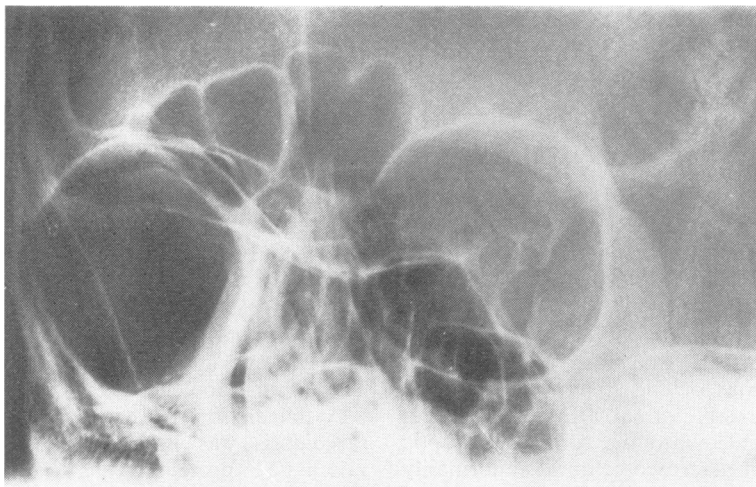


Fig. 3 Case 2. Axial view through left optic canal. Note cystic radiolucencies within sclerotic area in vicinity of slightly widened canal.

this eye. The examination was otherwise normal. There were no other neurological signs. Skull radiographs and a left carotid angiogram were read as normal.

Three months later, vision had deteriorated to counting fingers on the left, and the left optic disc was thought to be somewhat blurred. He was then referred to Sahlgrenska sjukhuset for further investigation. Ophthalmological examination confirmed the visual loss and the presence of a pale optic disc with slight oedema on the left. Skull films now disclosed irregular sclerosis of the medial parts of the left sphenoid wings, and cystic radiolucencies surrounded by a sclerotic ring close by the widened optic canal (Fig. 3). A pneumoencephalogram and isotopic brain scan were within normal limits.

Neurosurgical exploration via a left frontal approach disclosed a hyperaemic and coarsely textured anterior clinoid process. The left optic nerve was swollen in the region of the optic canal. Unroofing of the canal showed that the swelling had a length of about 20 mm. The deformed part of the nerve was resected.

Microscopic examination of the optic nerve and a small piece of dura mater from the anterior clinoid process showed infiltration by granulomatous tissue. In the dura mater the infiltration was diffuse, but in the optic nerve it was largely confined to the leptomeninges and interfascicular septa (Fig. 4). The meninges and septa were widened by infiltrating lymphocytes and plasma cells and by proliferation of reticulin fibres. There were also many tubercles formed of epithelioid

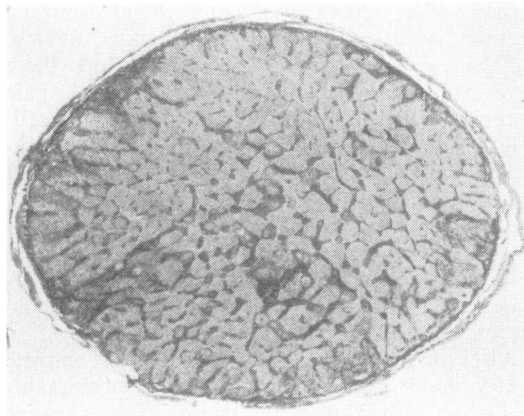


Fig. 4 Case 2. Section of optic nerve. There is granulomatous lepto-meningeal and interfascicular infiltration. In several regions the infiltrates extend into neural fascicles. Haematoxylin van Gieson, $\times 15$

and multinucleated giant cells (Fig. 5). Some of the granulomata had spread into the neural fascicles. A mild diffuse myelin loss was seen, with accentuation around larger granulomata. Some axons showed focal or terminal swellings. Glial cells frequently showed reactive changes but there was little glial fibre formation. There was no necrosis. No acid-fast bacilli or fungi were found.

The postoperative course was uneventful. A search for multisystem manifestations of sarcoidosis was made, but the only abnormality found was a few pinhead-sized rarefactions in the finger phalanges, of obscure aetiology. Unfor-

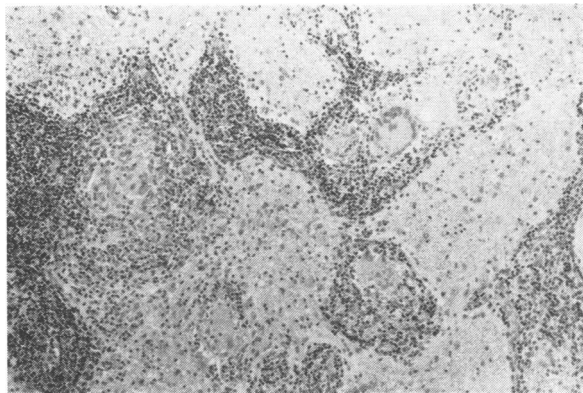


Fig. 5 Case 2. Section of optic nerve. Interfascicular tissues are infiltrated with lymphocytes and plasma cells, among which are seen granulomata composed of pale epithelioid cells and multinucleated giant cells. There is also local extension into nerve fascicles, in which glial cells are enlarged. Haematoxylin van Gieson, $\times 380$

unately, the patient refused follow-up examinations. He considered his health excellent at the last contact, seven years after surgery.

Discussion

Ingestad and Stigmar (1971) recently reviewed the various types of optic nerve lesions that have been encountered in sarcoidosis. They distinguished five different types: (i) optic disc oedema associated with uveitis or retinopathy of sarcoidosis, (ii) papilloedema from increased intracranial pressure, (iii) retrobulbar neuritis, (iv) optic atrophy secondary to compression from an intracranial sarcoid mass, and (v) primary granuloma of the optic nerve.

Of these various optic nerve lesions disc oedema and papilloedema are undoubtedly the most common. Retrobulbar neuritis has been recorded in a few instances (Colover, 1948; Morax, 1956; Walsh and Smith, 1968). Optic atrophy from a suprasellar sarcoid mass was the presenting sign in the patient described by Walsh and Smith (1968). The most common form of intracranial involvement of the optic nerve occurs with hypothalamic and chiasmal sarcoidosis, and is characteristically accompanied by endocrinological disturbances including diabetes insipidus (Aszkanazy, 1952; Blain *et al.*, 1965; Ingestad and Stigmar, 1971).

Primary granulomata of the optic nerve without involvement of the hypothalamus or the pituitary are probably the rarest of the optic nerve manifestations of sarcoidosis (Jampol *et al.*, 1972). Ten cases with probable sarcoid granulomata of the optic disc were recently reviewed by Laties and Scheie (1972), who added one case of their own. Statton *et al.* (1964) recorded an unique case of intraorbital optic nerve sarcoid masquerading as an optic nerve glioma. We have been able to cull

from the literature only two instances of microscopically identified sarcoid-like affections restricted to the intracranial optic nerve and its vicinity (Table). Alajouanine and coworkers (1952) described one case, which has been reported in greater detail also by Morax (1956). This middle-aged lady had suffered from pleurisy of undetermined aetiology. Progressive visual loss on the right prompted neurosurgical exploration. A small sarcoid granuloma was found on the surface of the intracranial optic nerve. The granuloma insinuated itself into the optic canal. The second case was recorded by Anderson *et al.* (1966). Their patient complained of frontal headache and decreasing vision on the right. There were no signs of systemic illness. There was slight proptosis on the right, and the right optic canal was enlarged radiologically. Craniotomy disclosed a meningioma-like tumour encircling the right optic nerve, extending into the optic canal and onto the floor of the middle fossa. Biopsy specimens were considered compatible with sarcoidosis on microscopic examinations.

Our two cases are remarkably similar to those previously reported (Table). In all instances there was unilateral visual loss without obvious signs of systemic illness. Visual loss was related to chronic granulomatous infiltration of dura mater within and adjacent to the optic canal. Changes in the surrounding bone were evidenced by radiological changes. It is interesting to note that the clinical diagnosis before and during operation was meningioma in at least three of the four cases. This is natural in view of the very high incidence of sphenoidal meningiomas in adults with these signs but other conditions are capable of producing similar pictures (Scott *et al.*, 1974; Hasso *et al.*, 1975; Lee, 1976).

The radiological picture of expansion of the bone with cystic sclerosis suggests focal destruc-

Table Summary of cases of sarcoidosis restricted to intracranial optic nerve and adjacent area

Author	Patient's age (yr)	Clinical symptoms and signs	Bone changes	Contrast studies	Cerebrospinal fluid	Distribution of abnormality	Systemic abnormality
Alajouanine <i>et al.</i> (1952)	55	Visual loss, disc oedema, 'electric shocks'	None	Not stated	Not stated	Optic nerve and canal	History of pleurisy, phlebitis post-op.
Anderson <i>et al.</i> (1966)	18	Visual loss, optic atrophy, proptosis, headache	Eroded optic canal	Normal	Normal	Optic canal, middle fossa	Increased gamma globulin in serum, myocarditis
Present case 1	70	Visual loss, double vision, Horner's syndrome, headache	Cystic sclerosis of medial ala minor	Faint 'blush' in superior orbital fissure, superior orbital vein occluded here	Barrier damage, immunopathy, inflammatory cells	Optic canal, ala minor	Increased alpha and gamma globulins in serum, relative cutaneous anergy
Present case 2	45	Visual loss, disc oedema, headache	Irregular sclerosis of optic canal	Air study normal	Normal	Anterior clinoid, optic nerve	None

tion of bone with reactive hypermineralisation. Such changes are not characteristic of meningiomas in this area. Meningiomas of the sphenoid wing usually produce a homogeneous sclerotic expansion of the bone. So-called 'blistering', a bubbly radiolucency within a hyperostotic area, is common with meningiomas of the planum sphenoidale but seems to be restricted to this particular location (Lee *et al.*, 1976). Widening of the optic canal and occlusion of the superior orbital vein are non-specific changes, as is marked tortuosity of a meningeal artery.

Neither of our cases presented distinctive evidence of extracranial sarcoid lesions, although more widespread involvement was suggested by raised levels of gammaglobulin in CSF and serum as well as relative cutaneous anergy in case 1. Our cases thus lacked a hallmark of sarcoidosis, the widespread involvement of organs. However, sub-clinical, extracranial sarcoid cannot be ruled out. Several previously reported cases of sarcoidosis clinically believed to be restricted to the brain have been found to have extracranial disease at necropsy (Urich, 1974). The unique case of orbital optic nerve sarcoid mentioned above (Stattin *et al.*, 1964) developed hilar enlargement three years after operation. Our cases have been followed for one and seven years, respectively, and have so far remained free from symptoms and signs suggesting extracranial involvement. Neither had signs of ocular sarcoid on repeated examination. The Kveim test has not been available.

Lack of symptoms and signs of multisystem involvement demands an examination of diagnostic histopathological criteria. Non-caseating epithelioid cell tubercles constitute the histopathological feature of sarcoid. A few tubercles may show a little central fibrinoid necrosis (Scadding,

1970). The tubercles found in the tissues of the nervous system resemble those seen in other organs. They consist of central pale epithelioid and multinucleated giant cells with a peripheral zone of round cells, chiefly lymphocytes. Inclusion bodies such as Schaumann and asteroid bodies may be seen centrally. The tubercles may resolve or proceed to hyaline fibrosis (Cares, 1972; Harri-man, 1976). Many authors have stressed the frequent perivascular location, and even direct vascular involvement, when sarcoidosis affects neural structures (Meyer *et al.*, 1953; Herring and Urich, 1969). Cranial nerve damage can occur from surface exudation, interfascicular invasion, ischaemia and compression.

Other disease processes which may provoke a granulomatous inflammation must be excluded (Höök, 1954; Drury, 1970; Cares, 1972; Nurick *et al.*, 1972). Reaction to intracranial foreign body seems extremely unlikely in our cases, neither of which had suffered severe head trauma or had undergone previous neurosurgery or neuroradiological examination. There was nothing to suggest beryllium poisoning. Tuberculosis and syphilis were actively ruled out, and the many years of good health after surgery in case 2 speak strongly against any type of infection, including a mycosis. From the histopathological viewpoint, giant-cell granulomatous angiitis is an important differential diagnosis in sarcoidosis of the central nervous system (Nurick *et al.*, 1972; Urich, 1974), but may be ruled out because of the lack of signs of progressive intracerebral disease or typical vascular changes. To our knowledge, bone changes have not been described in this disease. Other conditions which should be excluded, and for which there was no evidence in our cases, include allergic granulomatosis, Hodgkin's disease, and

connective tissue diseases (particularly polyarteritis nodosa and disseminated lupus erythematosus).

Our two cases do not meet the diagnostic criteria for any specific granuloma-provoking disease. They are similar to the two cases previously reported as examples of sarcoidosis (Table). Therefore, we consider our cases worthy of presentation. They raise again the problem of the correct classification of solitary lesions with histological features resembling sarcoidosis. Applying strict criteria, we view these as cases in which a sarcoid-like reaction, possibly an expression of true sarcoidosis, affected the region of the intracranial optic nerve and canal. As such, the cases under discussion show a comparatively uniform clinical and radiographic picture. It is possible that the present disorder is a variant of the much more common chiasmal/hypothalamic sarcoidosis syndrome mentioned above. It may also be viewed as another example of the infinite variety of the clinical expressions of intracranial sarcoidosis (Douglas and Maloney, 1973).

References

- Alajouanine, T., Ferey, D., Houdart, R., and Ardouin, M. (1952). Forme neuro-oculaire pure de la maladie de Besnier-Boeck-Schaumann. Amblyopie rapide par atteinte successive des deux nerfs optiques a un an de distance. *Revue Neurologique (Paris)*, **86**, 255-257.
- Anderson, W. B., Parker, J. J., and Sondheimer, F. K. (1966). Optic foramen enlargement caused by sarcoid granuloma. *Radiology*, **86**, 319-322.
- Aszkanazy, C. L. (1952). Sarcoidosis of the central nervous system. *Journal of Neuropathology and Experimental Neurology*, **11**, 392-400.
- Blain, J. G., Riley, W., and Logothetis, J. (1965). Optic nerve manifestations of sarcoidosis. *Archives of Neurology (Chicago)*, **13**, 307-309.
- Cares, R. M. (1972). Sarcoidosis and granulomatous encephalitis. In *Pathology of the Nervous System*. Volume 3, pp. 2422-2429. Edited by J. Minckler. McGraw-Hill: New York.
- Colover, J. (1948). Sarcoidosis with involvement of the nervous system. *Brain*, **71**, 451-475.
- Douglas, A. C., and Maloney, A. F. J. (1973). Sarcoidosis of the central nervous system. *Journal of Neurology, Neurosurgery, and Psychiatry*, **36**, 1024-1033.
- Drury, R. A. B. (1970). Problems in histological interpretation in sarcoidosis. *Postgraduate Medical Journal*, **46**, 478-483.
- Harriman, D. F. G. (1976). Bacterial infections in the central nervous system. In *Greenfield's Neuro-pathology*. 3rd Edition, pp. 252-253. Edited by W. Blackwood and J. A. N. Corsellis, Arnold: London.
- Hasso, A. N., Bentson, J. R., Wilson, G. H., and Vignaud, J. (1975). Neuroradiology of the sphenoidal region. *Radiology*, **114**, 619-627.
- Herring, A. B., and Urich, H. (1969). Sarcoidosis of the central nervous system. *Journal of the Neurological Sciences*, **9**, 405-422.
- Höök, O. (1954). Sarcoidosis with involvement of the nervous system. Report of nine cases. *Archives of Neurology and Psychiatry (Chicago)*, **71**, 554-575.
- Ingestad, R., and Stigmar, G. (1971). Sarcoidosis with ocular and hypothalamic-pituitary manifestations. *Acta Ophthalmologica*, **49**, 1-10.
- Jampol, L. M., Woodfin, W., and McLean, E. B. (1972). Optic nerve sarcoidosis. Report of a case. *Archives of Ophthalmology*, **87**, 355-360.
- Laties, A. M., and Scheie, H. G. (1972). Evolution of multiple small tumors in sarcoid granuloma of the optic disk. *American Journal of Ophthalmology*, **74**, 60-66.
- Lee, K. F. (1976). The diagnostic value of hyperostosis in midline subfrontal meningiomas. *Radiology*, **119**, 121-130.
- Lee, K. F., Whiteley, W. H., Schatz, N. J., Edeiken, J., Lin, S., and Tsai, F. Y. (1976). Juxtaseilar hyperostosis of non-meningiomatous origin. *Journal of Neurosurgery*, **44**, 571-579.
- Meyer, J. S., Foley, J. M., and Campagna-Pinto, D. (1953). Granulomatous angiitis of the meninges in sarcoidosis. *Archives of Neurology and Psychiatry (Chicago)*, **69**, 587-600.
- Morax, P. V. (1956). Les localisations neuro-oculaires de la réticuloendothéliose de Besnier-Boeck-Schaumann. *Annales d'Oculistique*, **189**, 73-91.
- Nurick, S., Blackwood, W., and Mair, W. G. P. (1972). Giant cell granulomatous angiitis of the central nervous system. *Brain*, **95**, 133-142.
- Scadding, J. G. (1970). The definition of sarcoidosis. *Postgraduate Medical Journal*, **46**, 465-467.
- Scott, T. V., Schatz, N. J., and Lee, F. L. (1974). Malignant pituitary adenoma. A cause of sphenoid hyperostosis and monocular blindness. *Archives of Ophthalmology*, **91**, 123-125.
- Statton, R., Blodi, F. C., and Hanigan, J. (1964). Sarcoidosis of the optic nerve. *Archives of Ophthalmology*, **71**, 834-836.
- Urich, H. (1974). Some outstanding problems in sarcoidosis of the central nervous system. In *Proceedings of the VI. International Conference on Sarcoidosis*, pp. 338-339. Edited by K. Iwai and Y. Hosoda. University Park Press: Tokyo.
- Walsh, T. J., and Smith, J. L. (1968). Sarcoidosis and suprasellar mass. In *Neuro-ophthalmology*, Volume 4, pp. 167-177. Edited by J. L. Smith. C. V. Mosby: Saint Louis.