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THE RIDDLE OF ENDOCRINE EXOPHTHALMOS

The picture of hyperthyroidism and exophthalmos has long been known,[1] yet true understanding of exophthalmos is still lacking in spite of recent researches into its pathophysiology.

Proptosis of endocrine origin is usually bilateral and often asymmetrical, but may remain localized to one side. A direct forward protrusion is said to be characteristic, as is peri-orbital thickening, oedema and early ophthalmoplegia. Papilloedema, optic atrophy and corneal ulceration are late events.

Exophthalmos is classically associated with Graves' disease, but this is not constant and the one condition may precede or follow the other. It may also manifest for the first time after surgical or radio-iodine therapy for hyperthyroidism, whether thyroid function is normal or low. Occasionally, endocrine exophthalmos occurs with no clinical evidence of thyroid disorder and though Brain would prefer to regard it as a distinct entity, the evidence points to its being part of a single thyroid disorder. Such evidence includes histological examination of retro-orbital tissue,[2] a very high incidence of elevated thyroidal ^{131}I uptakes,[3] and the presence of abnormal circulating hormones which appear to be common to all forms of this condition, irrespective of thyroid function.[4,5]

Both experimental and necropsy studies have shown the underlying pathogenesis to be an increase in orbital fat, round-cell infiltration, and subsequent fibrotic replacement.[2,6] Mast cells may be present, leading to the deposition of a muco-polysaccharide.[7] Exophthalmos results from the mechanical effects of these changes, which may be widespread and may affect ocular muscles (hence early ophthalmoplegia), skeletal muscle, kidney and liver.[8] Although the effects may be diffuse and suggest a systemic effect of a hormone or hormones, depot fat transplanted to the orbits does not develop the expected changes when exophthalmos is experimentally induced.[9] Thus a selective orbital reaction to the circulating substance responsible is possible.

The nature of such a substance has been in dispute for years. It was initially considered to be thyroxine, but thyrotrophin was later suggested because of the experimental induction of exophthalmos with anterior pituitary extracts rich in this hormone.[10] However, this concept was not consistent with the rarity of exophthalmos in spontaneous myxoedema where high levels of thyrotrophin would be expected. Subsequently, the circulating thyrotrophin level was shown to be completely unrelated to clinical exophthalmos by workers using biological techniques to assay the hormone.[11]

Since the exophthalmos induced experimentally by anterior pituitary extracts is not a result of thyrotrophin, another substance must clearly be implicated, and this is currently known as exophthalmos-producing substance (EPS). More direct evidence of the separate identities of EPS and thyrotrophin includes selective destruction of thyrotrophin by iodination at pH 4·2,[12] the demonstration of different mobilities on electrophoresis, and finally discrepant results after parallel assay for both substances on the same plasma sample.[13] EPS probably originates in the anterior pituitary, but may be present in the plasma of patients with progressive exophthalmos,[4,14] and is conceivably the agent responsible for the widespread fat-mobilizing effects referred to earlier. Assay techniques are at present crude and are based on the induction of measurable degrees of proptosis in experimental animals under carefully standardized conditions.[4,14]

Recently, a substance found in the plasma of patients with endocrine exophthalmos, irrespective of thyroid function, has been shown to possess definite thyrotrophin-like properties,[15] but exerts its effect on the thyroid gland in a delayed and sustained manner quite unlike 'true' thyrotrophin.[5,16] Because of this peculiarity it has been termed 'long-acting thyroid stimulator' (LATS). It differs from thyrotrophin in many of its fundamental properties. It has a longer half-life, a steeper dose-response slope,[17] migrates differently on starch-block electrophoresis,[15] is more stable, and finally has not been found in the anterior pituitary either in normal subjects or in exophthalmic patients in whom circulating levels had been demonstrated.[13,18]

The important question of whether EPS and LATS are one substance has recently been tackled, and parallel assays for both in single plasma samples have yielded discrepant results, suggesting their non-identity.[13]

The exact role of the two substances is far from clear. They may act independently or synergistically, or EPS may mediate its action *via* LATS, which may have its source in the end-organ. Of interest in this respect is the high level of LATS found in homogenates of pretibial myxoedematous tissue.[13]

The riddle of endocrine exophthalmos remains unanswered, but rapid advances in biochemical and assay techniques appear to be throwing open the door to our understanding of the pathogenesis; perhaps from this will emerge a rational therapeutic approach to a condition which remains debilitating and deforming.

1. Parry, C. H. (1825): *Collections from the Unpublished Medical Writings*, vol. 2.
2. Smelser, G. K. (1943): Amer. J. Physiol., **140,** 308.
3. Werner, S. C. *in* Astwood, E. B. ed. (1960): *Clinical Endocrinology*, 1st ed., p. 212. New York: Grune and Stratton.
4. Dobyns, B. M., Wright, A. and Wilson, L. (1961): J. Clin. Endocr., **21,** 648.
5. Munro, D. S. (1959): J. Endocr., **19,** 64.
6. Albert, A. (1945): Endocrinology, **37,** 389.
7. Asboe-Hansen, G. and Iversen, K. (1951): Acta endocr. (Kbh.), **8,** 90.
8. Dobyns, B. M. (1946): Surg. Gynec. Obstet., **82,** 609.
9. Smelser, G. K. and Ozanics, V. (1949): Amer. J. Ophth., **32,** 1557.
10. Schokaert, J. A. (1932): Amer. J. Anat., **49,** 37.
11. D'Angelo, S. A., Paschkis, K. E., Gordon, A. S. and Cantarow, A. (1951): J. Clin. Endocr., **11,** 1237.
12. Jefferies, W. M. (1949): *Ibid.*, **9,** 927.
13. Pimstone, B. L. and Hoffenberg, R. (1962): In preparation.
14. McGill, D. A. (1960): Quart. J. Med., **29,** 423.
15. McKenzie, J. M. (1960): J. Clin. Endocr., **20,** 380.
16. *Idem* (1958): Endocrinology, **62,** 865.
17. Adams, D. D. (1961): J. Clin. Endocr., **21,** 799.
18. McKenzie, J. M. (1961): *Ibid.*, **21,** 635.

GIF IN DIE KOFFIE

Onlangse bewerings van gif in koffie waar geen gif was nie, herinner aan pogings meer as 'n eeu en 'n half gelede om geen gif te vind nie waar daar wel gif was.

Die private lewe van Napoleon Bonaparte was alles behalwe privaat, soos beoordeel uit geskrifte oor sy lewe. Die laaste drie jaar van sy lewe is egter minder volledig gedokumenteer.

Napoleon is op 5 Mei 1821 oorlede. Volgens sy eie versoek is 'n na-doodse ondersoek op hom uitgevoer deur Francesco Antommarchi, sy Korsikaanse geneesheer, in die teenwoordigheid van 6 Britse geneeshere.

Dit is bekend dat Napoleon siek was tydens die grootste gedeelte van sy verblyf op St. Helena, en dit is moontlik dat dinge vir homself ook verdag was – vandaar sy begeerte vir 'n na-doodse ondersoek. Hierdie ondersoek het egter baie gissings en spekulasie gaande gemaak. Dit het klaarblyklik sy doel gemis, miskien weens gebrekkige integriteit van lede van die outopsie-span.

Die teenwoordiges het algemene instemmigheid gehad dat die maag veranderde bloed bevat het en dat die piloriese gebied ulserasie getoon het. Volgens dr. Shortt, die hoof mediese beampte van die eiland, was die lewer buitengewoon hard en groot, maar op bevel van die Goewerneur is dié sinsnede geskrap. Die rapport van die hoof mediese beampte en 4 ander geneeshere (een van hulle was nie teenwoordig toe die outopsie uitgevoer is nie), meld karsinoom van die maag as oorsaak van dood. Geen metastases is gewaar nie. Antommarchi, wat die ondersoek gedoen het, het geweier om die rapport te teken. Terug in Europa het hy 'n onafhanklike rapport ingedien tesame met 'n paar patologiese monsters, en vier jaar later het hy 'n tweede en teenstrydige verslag die lig laat sien.[1]

Vandag, na 141 jaar, is dit baie duidelik dat daar sekerlik 'n knoeiery om die dood en na-doodse ondersoek van wyle Napoleon was.

Die gerugte dat hy aan chroniese arseenvergiftiging oorlede is, het begin toe sy lyk 20 jaar later na Frankryk vervoer is en dit in 'n merkwaardig goeie toestand van bewaring gevind is.

Die wyse waarop die arseen toegedien is, het ook spekulasie laat ontstaan. St. Helena was berug vir lewersiektes, en dit is moontlik dat daar waterbronne met hoë arseeninhoud bestaan het.[1] Die moontlikheid dat rottegif (en St. Helena was ook deur rotte geteister) van 1820 as hoofbestanddeel arseen kon bevat, is ook genoem.[1]

Die twee (waarskynlike) slothoofstukke in hierdie geskiedenis is verlede jaar en vanjaar geskryf.

Met 'n baie gevoelige en betroubare aktivasie-tegniek kon Forshufoud, Smith en Wassén[2] aantoon dat 'n haarlok van Napoleon 'n totale hoeveelheid van 10·38 dele per miljoen arseen bevat het, teenoor die normale inhoud van 0·8 dele per miljoen. Die moontlikheid dat die haarlok dalk omgeruil was, is genoem[1] maar asof die waarheid die leuen doelbewus agterna ja, is daar 'n verdere reeks gebeure wat hierdie aspek bo twyfel verhef.

In November 1961, kort na die publikasie van die bogenoemde bevindings, het M. Clifford Frey homself by die Departement van Geregtelike Geneeskunde, Glasgow, aangemeld. Hy is 'n tekstielfabrikant van Münchwiler, Switserland, en hy het by hom 'n familie-erfstuk gehad bestaande uit 'n bondel van Napoleon se hare vasgeheg aan 'n stukkie papier met 'n ingewikkelde knoop. Die navorsers is toegelaat om 'n redelike hoeveelheid hare te neem, mits die knoop nie losgemaak word nie. 'n Aantal hare, die langste 13 cm., is verkry en dit is duidelik dat hulle met 'n skeermes afgeskeer is en nie met 'n skêr nie. Die koevert is gemerk *'Chevaux de l'immortel Empereur Napoleon'*. Die afsender van die brief was Abram Noverraz, en die datum in sy handskrif is duidelik leesbaar en stem ooreen met die datumstempel van die Lausanneposkantoor. Die geskiedenis van hoe die erfstuk in die Frey-familie beland het, word gegee.[3] M. J. Abram Noverraz was die lyfbediende van Napoleon sedert 1809. Hy het 'n reputasie gehad as 'n volkome betroubare man en was absoluut lojaal aan sy meester en sy nagedagtenis. Die aand na Napoleon se dood is sy kop geskeer met tweërlei doel: om aandenkings te verskaf en om die maak van 'n dodemasker te vergemaklik. Pertinent is egter die feit dat Noverraz die haarkapper was.[3]

Hierdie hare toon dat daar 'n piek, met konsentrasie van meer as 50% bo die gemiddelde vir die hele haar, tussen die 4 cm. en 8 cm. merk is (totale lengte 12 cm.) Hieruit kan afgelei word dat Napoleon vir 'n periode van 4 maande 'n abnormale hoë konsentrasie arseen ontvang het.[2] Te oordeel aan die enigste haar met 'n ongesnyde distale punt, kon die werkers verder vind dat die hoë konsentrasies nou korreleer met die ooggetuie-verslag van sy siekte wat deur verskeie remissies gekenmerk was.

Een van die outeurs het dan ook in 'n monogram[4] aangetoon dat die siekte van Napoleon op St. Helena chroniese arseenvergiftiging was, onderbreek deur episodes van akute arseenvergiftiging.

1. Annotasie (1961): Lancet, **2**, 1395.
2. Forshufoud, S., Smith, H. en Wassén, A. (1961):: Nature, **192**, 103.
3. Smith, H., Forshufoud, S. en Wassén, A. (1962): *Ibid.*, **194**, 725.
4. Forshufoud, S. (1962): *Who killed Napoleon?* Londen: Hutchinson.