

# **ENDOCRINOLOGY'85**

**Editors:**

**G. M. MOLINATTI  
L. MARTINI**

# ENDOCRINOLOGY '85

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Endocrinology '85, Torino, 5-8 June 1985

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In 1884 Fritsche and Klebs reported the clinical and pathological features of the first recognized case of acromegaly.

In 1886 Pierre Marie described this illness and gave it its present name.

Thus, 1985 may be considered the Centennial of Acromegaly, and, to celebrate this event, the International Congress "Endocrinology '85" was organized.

**Prof. G.M. Molinatti**  
**Prof. L. Martini**

## PREFACE

“Endocrinology 85”, an International Congress organized by the Department of Clinical Medicine of the Faculty of Medicine and Surgery of the University of Turin and the Institute of Endocrinology of the University of Milan, was meant, first of all, as a celebration of the centennial of the description of acromegaly by the French physician Pierre Marie (P. Marie: “Sur deux cas d’acromégalie, hypertrophie singulière non congénitale des extrémités supérieures, inférieures et céphalique”. *Rev. de Méd.* 6, 297–333, 1886), who also coined the word now universally used to refer to the disease. Along this theme, the first half of the Congress was devoted to problems dealing with acromegaly the disease, the physiology of the secretion of growth hormone and the clinical use of human growth hormone and growth hormone releasing factor.

In the opening lecture, Professor Molinatti reviewing the history of the description of acromegaly by P. Marie, called attention to earlier recognition of the disease as a probable entity by Fritsche and Klebs (*Ein Beitrag zur Pathologie des Riesenwuchses*, E. Fritsche and E. Klebs, F.C.W. Vogel publ., Leipzig, 1884, 89 pages) and an earlier and little known report by the Italian Andrea Verga in 1864 (*Rendic. Reale Istituto Lombardo di Sci. e Lett.*, Vol. 1, 28 April 1864, pp. 111–118) who had called the disease “prosopectasia”. Verga had also recognized, at autopsy, the presence of a large pituitary tumor and may have come closer than any one of these early observations in implying a relationship between the pituitary tumor and the appearance and development of the disease. Let us not forget that in 1885 and earlier, no one had any clear concept of a function for the pituitary gland. Indeed, Pierre Marie’s description of acromegaly is often quoted as an example of a correct observation (a pituitary tumor accompanies all cases of acromegaly) erroneously interpreted (the features of acromegaly appear when a pituitary tumor destroys the function of the gland, therefore the normal function of the gland is to inhibit somatic growth) (see *Textbook of Endocrinology*, Hans Selye, *Acta Endocrinologica Publ.*, Montreal, Canada, 1947, p.197; also Aschner, B. *Über die Funktion der Hypophyse*, *Pflüger’s Archiv. für Physiologie*, 146, 1–146, 1912 p. 120). Actually a search of the literature under the name of Marie and collaborators by the writer of this short preface has failed, so far, to uncover the statement by Marie that would justify Selye’s or Aschner’s critique. Indeed the text of the reference quoted by Aschner as the basis for his comments on Marie’s hypothesis (P. Marie and G. Marinesco, “Sur l’anatomie pathologique de l’acromégalie, *Arch. de Méd. Expér. et Anat. Path.* 2, 539–565, 1891) does not contain any statement by the authors relating functionally the pituitary tumor and the disease of acromegaly, and even less so, any statement proposing a physiological function for the normal pituitary gland.

Indeed, a recurring question as asked by Fritsche and Klebs, as well as Pierre Marie and Marinesco, is whether the “hypertrophy” of the pituitary is simply another example of the general hypertrophy of soft tissues, and the splanchnomegaly that was recognized as part of the clinical syndrome of acromegaly. It was the merit of Aschner to show unequivocally that total hypophysectomy when properly and suc-

cessfully completed (by the transpalatal approach he developed in dogs) first, is compatible with long term survival of the animal, and second, leads to arrests of the (normal) growth process (Aschner, B. op.cit.). As we all know now, it was not until 40 or 50 years later that it was realized that chronic administration of rather crude pituitary preparation enriched in growth hormone by Herbert Evans and his colleagues, would produce the peripheral modification of tissues and organs known to be part of the syndrome of acromegaly (H.M. Evans and J.A. Long (1921): The effects of the anterior lobe of the hypophysis administered intraperitoneally upon growth and the maturity and oestrus cycles of the rat *Anat. Rec.* 21, 61-63).

While we now understand the physiopathology of acromegaly, what of its treatment? This was discussed at great length both in the opening lecture of Professor Molinatti with eclectic proposals of choices between surgery and several modes of irradiation, administration of ergot derivatives or somatostatin-analogs, and in one aspect or another in several of the other presentations dealing with the control of growth hormone secretion (Besser, London; Guillemin, La Jolla, California; Lamberts, Rotterdam; Porter, Dallas, Texas and Massara, Turin) or its mechanism of action (Van Wyk, Chapel Hill; Rudman, Chicago).

The recently characterized hypothalamic hypophysiotropic peptide GRF (growth hormone releasing factor) was discussed extensively from the clinical point of view, for its role in acromegaly due to its possible ectopic production (carcinoids, tumor of the pancreas, etc.) (Besser, Guillemin), also regarding its use as a diagnostic agent of differentiate between hypophysial hypopituitarism and hypothalamic (or suprahypophysial) hypopituitarism and finally as a therapeutic agent in the pertinent cases of hypopituitarism and growth retardation. The cellular mechanisms of action of growth hormone releasing factor was discussed extensively (Cronin, University of Virginia). Thirty or so presentations dealt with other aspects of adenopituitary functions (use of recently developed analogs of somatostatin, control of secretion of prolactin, effects of CRF-corticotropin releasing factor, clinical tests with growth hormone releasing factor, locus of action of somatomedins on pituitary functions, endorphins on growth hormone and prolactin secretion, mode of action of androgens, etc.). A lecture (Tanner, London) discussed the source of the recently recognized problems of degenerative cerebral disease in 3 (American) and 1 (British) patients (pituitary dwarf) who had received some on the earliest preparation of human growth hormone.

The other aspect of the Congress, for about equal time, dealt essentially with the endocrine control of calcium homeostasis. This was highlighted by several lectures, one by MacIntyre (London) on calcitonin and the recently characterized peptide CGRP (calcitonin-gene-related peptide) from knowledge of the structure of the calcitonin-gene-CGRP; calcitonin-gene-related peptide (CGRP) has now been seen in tissues, with a remarkable distribution in the brain; its powerful effects as a vasoactive agent were extensively discussed. DeLuca, Madison, Wisconsin, discussed the role of the hormones of the "vitamin D" series as they interrelate physiologically and in various pathological conditions with the Ca-regulating peptides, parathyroid hormones and calcitonin. Recent data on the isolation of the (porcine) receptor for 1,25-dihydroxy-

vitamin D<sub>3</sub> as well as the molecular biology of gene-regulation involving hormones of the vitamin D system were also discussed. Mazzuoli, Rome, discussed the involvement of parathyroid hormone in normal and pathological control of Ca metabolism, and Gennari, Siena, presented an overview of the current concepts on the management of osteoporosis.

A last aspect of the Congress dealt with the large question of the therapeutical approach to endocrine-dependent tumors (Brodie, Baltimore), the dynamics of the transport of protein-bound hormones into tissue (Partridge, Los Angeles) and the prostaglandins in reproduction endocrinology (Fuchs, New York).

With close to one hundred posters discussing the subjects already mentioned above plus gastrointestinal hormones, pharmacology of dopaminergic agents, transport of thyroid and steroid hormones in blood, prostaglandins, and endocrine-dependent tumors, "Endocrinology 85" was an informative, well organized, well balanced meeting.

**Roger Guillemin**

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## ACROMEGALY: A CENTURY LATER

GIAN MICHELE MOLINATTI

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Acromegaly was the first pituitary disorder to be recognized. Although the first known case was possibly that of the Egyptian king Akenaten in 1365 B.C., it was only in 1884 that Fritzsche and Klebs (1) described the main pathological features of a well-documented case of acromegaly. Two years later Pierre Marie (2) gave an extremely accurate description of the disease, which he had observed in 2 patients at professor Charcot's clinic in Paris. After careful perusal of 5 clinical reports previously published by different Authors who had given each a different name to 5 possible cases of the same disease, he suggested the term which we still use today.

However, careful historical research points at the Italian Andrea Verga as possibly the first to describe an unmistakable case of acromegaly. His report was published as early as 1864 in the "Rendiconti del Reale Istituto Lombardo di Scienze e Lettere" (3) but had probably remained unknown to Pierre Marie, as it has to most of us.

"Since 1860, while visiting the chronic patients admitted to the church of Santa Maria ai Nuovi Sepolcri, one of the houses subsidiary to the Ospedale Maggiore of Milan, I had been impressed by the look of one patient, whose waxy pallor and disproportionately large face was almost frightening. The low personnel serving in the that ward must have been similarly impressed, as they had nicknamed the woman 'big-face'. Seeing that I was staring at her, she told me how she once had not been ugly and looked just like the other girls".

Dr Verga proceeded to collect the patient's history, the most remarkable parts of which he reported as follows:

"Menses started at age 11... and ceased for good at 25. She married but had no children". At 35 years "... she started to realize that all parts of her body, which used to be rather thin, were progressively enlarging so that three times she had to have the rings on her fingers cut and, in particular, that her face was becoming monstrous. Admitted to the hospital for gastric fever on the 24

august 1856, she was declared chronic for rheumatism and amblyopia on the 16 september of the same year. Ever since, her sufferings, severe joint pain in particular, have not abandoned her".

The patient died from typhus in 1862 and a postmortem was performed.

"The skull was opened and some bloody fluid flowed out of it. The most outstanding feature was a tumor, the size of a large walnut, lying over the sella turca, pressing on and displacing the optic nerves and the mammillary processes and rooting with some peduncles within the sphenoid body. The pituitary gland was not found and one wonders whether it disappeared under pressure from the tumor or the tumor itself was but a degeneration of the gland".

"... The heart volume was twice as normal..."

"... Nothing in the abdomen, apart from liver hypertrophy..."

"... The skull was... of coarse dimensions, the exaggeration of which is evident in the face and especially in the maxillary bones".

"... The sella turca severely deformed and defective ...".

Discussing these findings, Dr Verga went on to suggest how "even in the explanation of the peculiar disease I have described the old concepts of humoral pathology may be applied. After a natural outlet (i.e. menstrual bleeding) had ceased, the humours... directed themselves elsewhere... to nourish and develop the whole body... I say all the body's parts because lengthening and thickening of the bones was accompanied by development of the soft parts adjacent to them or contained in their cavities".

"... It can be seen how the bones were driven by some internal power... to lengthen and dilate and, at the same time, to move away from each other. However, this, is true particularly of the face... and therefore I consider this a beautiful and exceedingly rare case of "prosopectasia" (from προσωρον = face, and εκτασις = extension, lengthening).

Verga added one final speculation: "... Prosopectasia can only take place at the age where the body has reached its maximum development, that is around 40 years... had the tendency to enlargement been earlier and more generalized, the result would probably be a female giant to be exhibited to the public as an extraordinary phenomenon".

Our tribute to Dr Verga's clinical acumen would probably be unreserved had

he seen the connection between the general symptoms and the pituitary tumor. However, this is probably asking too much of him and the medical knowledge of his time. He was probably mostly impressed by the facial deformities and concluded his paper by stating that "prosopectasia" may occur without causing severe disability as visual problems and joint pains, which were responsible for his patient's admission as a chronic patient to hospital, "appeared to have been induced, the first by the tumor sitting on the pituitary fossa and the second by an affection of the spine which remained undefined because its cavity had not been opened".

In contrast with Wass (4), who attributed to Minkowsky, in 1887 (5), the first report of pituitary enlargement among all the carefully assessed cases of acromegaly, it appears that Verga's anatomical and clinical description of the disease was indeed the first one.

In 1909, Crowe, Cushing and Homans demonstrated that complete pituitary removal is generally lethal in the dog and that growth is retarded in the few animals that survive (6).

Evans and Long reported in 1921 (7) in "Anatomical Record" the discovery of growth hormone, although at the time it was not known as such. In his Harveian Oration of 1924 Evans stated that "the anterior hypophysis is indispensable for growth to adult stature and a lessened amount of its hormone being a direct cause of an important group of, if not all, endocrine dystrophies and an increased amount of the hormone being a direct cause of overgrowth" (8).

Many years later, Li and Evans announced the isolation of growth hormone from bovine hypophysis in a highly purified form (9) and demonstrated that growth could be restored in hypophysectomized rats by administration of this substance (10).

It was of some disappointment that a pituitary dwarf, reported in 1950, did not go into positive nitrogen balance with growth hormone. An explanation for this was found in 1956, when human growth hormone was first purified (11). Human growth hormone was found to be substantially different from its bovine counterpart and it is now known that growth in primates follows only administration of the primate hormone (12).

The development of a radioimmunoassay for growth hormone has been of great

clinical relevance (13,14) as it has enabled us to gain further insight into the physiology and the pathophysiology of its secretion.

#### CLINICAL ASPECTS

In contrast with Verga's conclusion we now know that, if not adequately treated, acromegaly is accompanied by high morbidity, slow and progressive modifications of the physical appearance, impairment of the ability to work and premature death (15,16).



Fig. 1

Early diagnosis is difficult because of its slow development. Fig. 1 shows the photographs of a patient of ours during the 20 years preceding the diagnosis. If we carefully examine the face of this woman, we may perhaps see the first changes in the 1968 picture. These modifications became more evident in the following years. However, the diagnosis was made in 1979, when severe headache began.

Enlargement of the heart occurs in the absence of cardio-vascular disease or hypertension (17-20).

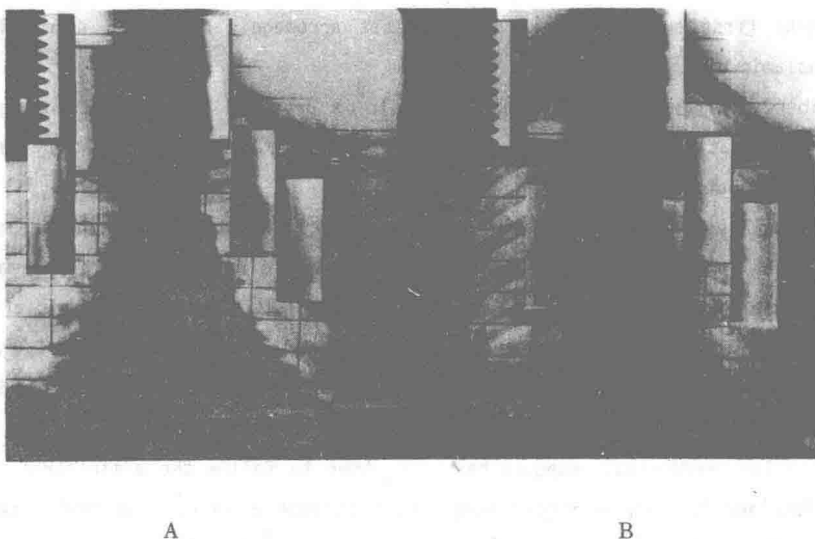


Fig. 2

Fig. 2A shows a typical case of heart enlargement in a 38 year old patient who had been acromegalic for at least 6 year and had no hypertension or heart disease. Fig. 2B shows the same heart returned to normal dimensions 6 months after normalization of GH obtained by intrasellar implant of  $^{90}\text{Y}$ . Electrocardiographic changes often accompany this situation, which may revert to normal if GH is normalized by therapy (21).

Enlargement of the lungs and poliposis of the colon are also commonly observed and the latter may represent a risk factor for the development of cancer (22).



Finally, diabetes mellitus may occur in 15-30% of patients (23) and the enlargement of the tumor may produce endocrine problems due to damage of the hypophysis or of the suprasellar structures.

#### PATHOGENESIS OF ACROMEGALY

Biological and clinical evidence suggest that GH-secreting pituitary tumors may be caused either by a primary pituitary disorder, an alteration in hypothalamic control, or a combination of both factors (24). Cryen and Daughaday first suggested in 1969 (25) that acromegaly may be a primarily hypothalamic disorder.

Evidence in favour of a hypothalamic role is provided by a study showing how the pulsatile GH secretion pattern of normal subjects is lost in some acromegalic patients.

Abnormal responses to inhibitory or stimulatory pathological manipulations have been also observed. For instance, these patients do not show the normal suppression of GH levels after a glucose load (26), and sometimes exhibit a paradoxical increase (27), whereas thyrotropin-releasing hormone (TRH) and luteinizing hormone-releasing hormone (LHRH) may stimulate a release of GH (28,29) a phenomenon that never occurs in normal subjects.

A similar paradoxical response has been shown to follow the administration of L-dopa and some dopaminergic drugs which produce a marked and protracted fall of plasma GH levels in some patients with acromegaly.

The situation is further complicated by the evidence of different responses to the inhibitory effect of somatostatin. This hypothalamic factor has been shown to inhibit GH secretion in response to various stimuli as well as in basal conditions in acromegalic subjects (30). Hanow et al. (31) and Pieters et al. (32) demonstrated the existence of two distinct groups of acromegalics characterized by their different sensitivity to somatostatin, which does not parallel the responses to bromocriptine.

These results gave support to the idea that some patients have an autonomously-functioning pituitary adenoma while in others primary hypothalamic malfunction may be involved (33). Some Authors, after studying the TRH- and bromocriptine-evoked responses of GH, suggested that both these