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This Week's Citation Classic

Thorner M O, McNeilly A S, Hagan C & Besser G M. Long-term treatment of galactorrhoea and hypogonadism with bromocriptine.
Brit. Med. J. 2:419-22, 1974.
[Medical Professorial Unit and Dept. Chemical Pathology, St. Bartholomew's Hospital, London, England]

Seventeen women and four men with galactorrhea and associated hypogonadism were treated with bromocriptine for two to 28 months. Serum prolactin levels were elevated in 12 of 17 patients. Bromocriptine therapy led to cessation of galactorrhea, lowered prolactin levels to normal, and restored gonadal function. [The *SCI*® indicates that this paper has been cited in over 330 publications since 1974.]

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"Prolactin is secreted by the anterior pituitary gland. Until 1971 many eminent physiologists did not accept that prolactin existed as a distinct and separate hormone from growth hormone in the human. The pioneering work of Friesen[1] finally led to the extraction of prolactin from the human pituitary. This prolactin was then used to raise antibodies to prolactin for the development of a radioimmunoassay for human prolactin. The radioimmunoassay was immediately used to measure prolactin levels in various physiological and pathological conditions. It became rapidly apparent that elevated circulating prolactin levels were often found in patients with galactorrhea and hypogonadism. At the same time, Flückiger[2] (working at Sandoz, Basel) had developed bromocriptine, an ergot drug, with specific prolactin lowering properties which acted directly at the pituitary to lower the prolactin levels.

"Some of the first clinical studies with bromocriptine in hyperprolactinemic patients were performed at St. Bartholomew's Hospital in London by G. Michael Besser.[3] The study which became this *Citation Classic* was the follow-up of that study; a larger group of patients was carefully studied before, during, and after withdrawal of treatment. Twenty-one patients were treated for up to 28 months. Included in this group were nine patients with pituitary tumors and their prolactin levels also fell to normal and gonadal function was restored.

"This paper demonstrated several important points: (1) hyperprolactinemia, irrespective of the presence of a demonstrable pituitary tumor, can be effectively treated by bromocriptine; (2) gonadal function, which is disordered in hyperprolactinemic states, is restored to normal in the majority of patients when prolactin levels are restored to normal; (3) gonadotropin secretion in hyperprolactinemia may be disordered due to a hypothalamic defect. Although at that time we believed that prolactin might induce hypogonadism by acting at the gonadal level, we now believe that it causes hypogonadism predominantly by interfering with gonadotropin-releasing hormone secretion at the hypothalamic level.

"The year 1974 was a crossroads for the understanding of hyperprolactinemia and the mechanism of action of bromocriptine at the pituitary level. MacLeod[4] had shown in 1969 that catecholamines could inhibit prolactin secretion *in vitro* at the pituitary level. The explanation for the widely observed direct inhibition of prolactin secretion by ergot drugs, including bromocriptine, only appeared after 1974 when the following observations were made: (1) bromocriptine inhibited dopamine turnover in the brain; (2) the inhibition of prolactin secretion by ergots could be blocked with neuroleptic drugs; and (3) dopamine receptors were identified in the pituitary and bromocriptine and other ergots had high affinity for these receptors.

"I believe the reason our paper is a *Citation Classic* is that it showed, for the first time, in a large group of patients, that medical therapy of hyperprolactinemia is effective in the long term. In recent years it has become clear that this therapy is also effective in reducing the size of these tumors and is becoming the treatment of choice for large prolactin secreting tumors. For a more recent review, see *Bromocriptine: A Clinical and Pharmacological Review*."[5]

1. **Hwang P, Guyda H & Friesen H.** A radioimmunoassay for human prolactin. *Proc. Nat. Acad. Sci. US* 68:1902-6, 1971.
2. **Flückiger E & Wagner H.** 2-Br-α-ergokryptin: beeinflussung von fertilität und laktation bei der ratte. *Experientia* 24:1130-1, 1968.
3. **Besser G M, Parkes L, Edwards C R W, Forsyth I A & McNeilly A S.** Galactorrhoea: successful treatment with reduction of plasma prolactin levels by brom-ergocryptine. *Brit. Med. J.* 3:669-72, 1972.
4. **MacLeod R M.** Influence of norepinephrine and catecholamine-depleting agents on the synthesis and release of prolactin and growth hormone. *Endocrinology* 85:816-923, 1969.
5. **Thorner M O, Flückiger E & Caine D B.** *Bromocriptine: a clinical and pharmacological review.* New York: Raven Press, 1980. 181 p.