

Besser G M, Parke L, Edwards C R W, Forsyth I A & McNeilly A S.

Galactorrhoea: successful treatment with reduction of plasma prolactin levels by bromocriptine. *Brit. Med. J.* 3:669-72, 1972.

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This paper was the first to report that the ergot alkaloid derivative 2-bromo- α -ergocryptine (bromocriptine, CB154, Sandoz, Basel) could be used to treat galactorrhoea; and it showed, using prolactin bioassay and radioimmunoassay, that the drug reversibly lowered elevated circulating prolactin levels. These initial observations were soon confirmed, and the drug has been in regular use worldwide since that time. [The *SCI*® indicates that this paper has been cited in over 335 publications.]

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Prior to 1970 most authorities in the world believed that prolactin did not exist as a human pituitary hormone separate from growth hormone, which was thought to be responsible for all the pituitary lactogenic activity. However, towards the end of the 1960s, many researchers became dissatisfied with this view. We had seen patients with pituitary tumours who had inappropriate lactation and hypogonadism without signs of growth hormone excess.

We were fortunate to make contact with Isabel Forsyth of the National Institute for Research in Dairying, Shinfield, England. She had a bioassay for animal prolactin using a rabbit breast preparation that could be induced to lactate in nonproliferative culture. Forsyth collaborated with us, and we showed that lactogenic activity could be demonstrated in the serum of 14 of 20 patients with inappropriate lactation and hypogonadism.¹ Appropriate control studies left us with the conclusion that the activity had to be due to prolactin. At exactly the same time, similar work using a mouse breast bioas-

say was being carried out by A.G. Frantz at Columbia University, New York.²

Following the publication of our paper, we were contacted by Sandoz of Basel, Switzerland. Edward Flückiger, a senior pharmacologist and endocrinologist there, had long believed that it would be shown that prolactin existed in the human. Flückiger, an expert in the field of ergot alkaloids, showed that the ergot mixture ergotoxin could lower rat prolactin, that the less toxic derivative 2-bromo- α -ergocryptine (bromocriptine) was equally effective, and that the action was directly on the pituitary in the rat.³ Flückiger realised the therapeutic potential of this compound. We gladly accepted the offer of Sandoz to investigate this drug. The five patients reported on in this paper were the first in whom it was shown that, as the drug was given, galactorrhoea disappeared and hypogonadism reversed, accompanied by a rapid reduction of the elevated serum prolactin levels to normal. The effects were indeed dramatic.

We later realised that prolactinomas were very common and that truly functionless tumours were much less frequent than had been previously thought. Even though female patients had been infertile and amenorrhoeic or male patients impotent for many years, administration of bromocriptine frequently resulted in the return of normal gonadal function within a few weeks. These patients became highly fertile. Furthermore, the tumours could be made to shrink in over 80 percent of such cases, and medical treatment now often replaces surgery.

When first introduced, we did not know how bromocriptine lowered prolactin, but it was later shown that bromocriptine was a long-acting dopamine agonist and that activation of dopamine receptors on the pituitary cells directly inhibits prolactin secretion.⁴ In the mid-1970s it was also shown that bromocriptine lowers growth hormone levels in a proportion of acromegalic patients with resolution of the acromegalic syndrome. This has been shown to be effective in long-term treatment.⁵

Introduction of this compound marked an interesting coincidence, since it is most unusual for a new hormone to be discovered at the same time as the treatment for its disturbed secretion. This remarkable circumstance led to a dramatic advance in the understanding of the physiology of the pituitary-gonadal axis, and the story is a great tribute to the original developer of the compound, Flückiger.

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