

Puberty blockers: a blight on the brain?

Centred on the University of Lille, France, in September 2022, a group of international researchers reported in the prestigious journal, *Science*, that the progressive devolution in mental abilities of people suffering from Down Syndrome (DS) could be attributed to an associated reduction in the production of a particular hormone. They based their assertion on the results of experiments they had performed undertaking on genetically engineered mouse models of DS and on a small group of adult human sufferers of DS in all of which the levels of the hormone had been restored to normal by various experimental means¹

The researchers report 'rescue' of cognition by replacement of that hormone and suggest the process may have a positive role in the treatment of other neuro-degenerative disease such as Parkinson's disease, and even ageing.

Reassuringly, the Lille researchers are not isolated in their findings. Recently, researchers in Iran have also found protective effects of that hormone against the development of Alzheimers-like disease in other rodents. The Iranians conclude the hormones fulfil this role by stimulation of local production of the sex hormone, oestrogen, which improves working memory and recognition of novel objects, while decreasing anxiety. The authors also suggest the experimental hormone 'might be a promising candidate' for use in humans².

The suggestions may be of profound importance: do they portend a quantum leap in medical care? To inhibit neuronal decay would surely be as significant as Howard Florey's finding that *Penicillium* mould inhibited bacterial growth. While it is a bit hard to be that optimistic, any improvement in the cognition of people with DS would be more than welcome.

Nevertheless, the Lille and Tehran findings may not be as welcome as one might imagine because the hormone in question is Gonadotrophin Releasing Hormone (GnRH) which plays a defining role in the process of reproduction as well as a 'non-reproductive' role in the process of brain development and maintenance of function. Its reproductive role is deliberately 'blocked' by medical practitioners committed to hormonal 'affirmation' of a confused child to a gender incongruent with biological sex. In the same process, however, its non-reproductive, neurological role is also interrupted.

The contradiction bears repeating. Researchers have found deficiency of GnRH in the brains of DS sufferers is associated with progressive cognitive decline, but the process may be 'rescued' by its replacement. They point to a necessary neuro-modulatory role of GnRH in the development of the brains of men and mice.

Conversely, proponents of hormonal 'affirmation' of a child (perhaps as young as 9 years of age) to a gender incongruent with chromosomes, deliberately administer compounds that 'block' the production of GnRH (and, thus, puberty), in the claim the process will provide more time for appropriate cognitive appraisal of identity, the process of puberty, the role of sex hormones, the implications of gender surgery, and the loss of sexuality including sensation and procreation.

Disregarding the question of whether any child possesses sufficient maturity of cognitive power to digest and responsibly act on such complicated, life changing matters, even if cognition is not limited by drugs, it should not be forgotten the brains of almost all gender confused children are also burdened by associated neurodevelopmental challenges such as autism, and lasting traumas of social disruption^{34 56}

Down Syndrome (DS).

DS is a constellation of abnormalities associated with possession of three whole (or parts) of the 21st chromosome (as aligned in size under the microscope) when there should only be one intact pair. The result of the extra 'gene dosage' (called a trisomy) confirms that 'too many chefs spoil the broth': imperfect direction is provided for formation of the face and other structures, including the brain. As a result, the DS brain is smaller and grows more slowly than normal: its neurons lack connecting fibres, their layers are thin, and regional connectivity is reduced. Worse, there is a progressive decline in function with ageing, associated with the appearance of Alzheimer-like abnormalities in almost all by the age of 40.

The Lille researchers report this decline is due to progressive reduction in the amount of GnRH produced in the brain, resulting from perturbation of a 'switch' in the cascade of compounds that initiates production of GnRH from its genetic base, and guides its transformation through several developmental stage until the active form is released. Excess gene dosage from the 'trisomic' 21 is held responsible for the perturbation.

No-one knows wherein lies the 'biological clock' that initiates the formation of GnRH, nor where in the brain the cascade actually begins but, as well as directing the formation of GnRH, the switch should permit a surge of GnRH in the months after birth (known as mini-puberty), then another surge some 10 years later to bring about puberty, then emission of GnRH in a sex specific way during reproductive life, to finally wither with senescence. Instead, the imperfect switch results in production of insufficient GnRH, interfering with mini and real puberty and reproductive capacity. Further, because of the 'non-reproductive role' of GnRH in the development of the brain and maintenance of neuronal integrity, the reduced production of GnRH would lead to progressive impairment of brain function.

The reproductive role of GnRH.

GnRH is produced by cells that originate in the part of the early embryonic face that is destined to become a nose. Then, travelling with cells destined for sensation of smell, they migrate under various chemical and other guides into the brain where most of the GnRH producing cells take up residence in the hypothalamus. Others migrate widely throughout the cortex and cerebellum. As suggested by the presence of their specific receptors, some may travel, or exert their influence, far beyond the brain, even into the walls of the intestine⁷.

Those GnRH producing cells residing in the hypothalamus extend branches in various directions, including to the pituitary gland (which secretes hormones) and to the limbic system (which co-ordinates cognition, emotion and memory, resulting in executive function). They may also release GnRH into the cerebro-spinal fluid as a way of influencing cells bearing their receptors in more distant parts of the central nervous system.

Perhaps the impact of GnRH cells on the pituitary gland is best known because it is basic to reproduction. In this process, GnRH is secreted in pulsatile fashion from the hypothalamus into the private blood system that encircles the pituitary gland to be carried to special cells in that gland that bear its receptors. When it docks with these receptors, the combination is taken into the cells to activate their nuclei to produce two hormones, named Follicle Stimulating Hormone (FSH) and Luteinising Hormone (LH) which are, in turn, released into the general blood stream to be conveyed to the gonads where they induce the production of ova and sperm, and the sex hormones, oestrogen and testosterone, which evoke secondary sexual characteristics in body and brain, of females and males. Thus, the name Gonadotrophin Releasing Hormone (GnRH) is derived from the

Greek for inducing development in organs associated with reproduction through the release of FSH and LH by the pituitary gland.

However, the gonadal effect of GnRH is not its only role in reproduction. For almost 50 years it has been known that a centre in the midbrain of rodents is also activated by GnRH: If artificially stimulated before puberty, the female will prepare for mounting, and the male to oblige. If 'blocked', this sexualisation is abolished⁸⁹¹⁰¹¹¹².

Furthermore, a 'ram' effect, also dependent on GnRH, has been observed in sheep in whom merely 'socio-sexual' communication with a mature male may be sufficient to induce ovulation in ewes¹³¹⁴.

Thus, GnRH evokes sexuality by primary effects within the brain, and by secondary effects upon the brain by sex hormones released from the gonads. Thus, even if the brain of an affected child were intact, it is biologically implausible to expect maturation of the child's sexual identity after 'blocking' the production of GnRH and thus neutering the child from sexual orientating, stimulating hormones.

The ability to block the function of GnRH was discovered soon after the elucidation of its structure of in the 1970's when chemical engineering permitted manufacture of slightly different compounds (analogues) which, if injected, would 'dock' with GnRh receptors and be taken into the cells to begin their designated function, but the analogues would not disengage from the receptor thus preventing its return to the surface to welcome succeeding arrivals of GnRH, expected every 90 minutes or so. Thus, blocking the return of the receptor would block the production of FSH and LH, with the 'knock on' effect of blocking the production of sex hormones by the gonads.

This was therapeutic, for example, for men whose testosterone was stimulating prostate cancer, and for women whose oestrogen was stimulating endometriosis. From these conditions, blocking analogues of GnRH were used to inhibit puberty when it was occurring precociously, and then, emerging from gender clinics in The Netherlands, it was used to block puberty in children confused over gender. Of course, blockers obstruct both reproductive and non-reproductive roles of GnRH.

Minipuberty: the first manifestation of GnRH's non-reproductive role?

As mentioned, soon after birth, in both rodents and humans, there is a surge in the production of GnRH which, acting on the gonads, results in a marked secretion in sex hormones: But why? Traditional explanation declares it initiates maturation of the sex organs and, in one sense, that might be correct: the production of ova begins that early in females. But the findings of the Lille researchers point in another direction: the surge in production is integral to the surge in brain growth and development known to occur in those months. Indeed, brain size increases by some 60% in those months, associated with marked development in function.

I was recently musing about this development in function when performing ultrasound examinations of the hearts of two normal and one DS affected infant, all of whom were about 6-8 weeks of age. The non-DS babies submitted me to intense visual interrogation. I could almost hear them thinking 'who is this stranger? What is he up to? Is he friend or foe? Do I like what he is doing?' Then, one decided in the affirmative and displayed a broad grin of approval. The other, however, decided I was up to no good and began to push me away with his hands. When that did not work, he curled up his legs to co-ordinate rejection with his arms and, when that did not work, he decided he would yell for his mother. All that development, in only 6 weeks from relative oblivion in the womb!

Sadly, the DS baby was uninterested, as are most babies after birth. Worse, his head circumference was smaller than normal and not growing normally.

In conversation in Lille, in the light of their studies, there was agreement with the concept that the surges of GnRH in 'mini-puberty' are involved with the developments in the brain that occur in that period. In other words, they represent the non-reproductive role of GnRH in brain development. Though not discussed in Lille, the acceleration of cognitive powers that ensue from puberty may also be considered similarly to represent the non-reproductive role of GnRH in brain growth.

The non-reproductive role of GnRH in older mice models of DS.

The Lille workers demonstrated that 'cognitive performance' in DS models of mice improved with replacement of GnRH. Using ultra-sophisticated techniques including the transplantation of GnRH producing cells into the brain of the DS mice and standard assessments of the cognitive powers of mice eg recognition of new objects, the researchers found cognition was improved by replacement of GnRH. Conversely, they confirmed that 'silencing' of GnRH production in normal mice was followed by cognitive loss.

The role in adult human DS sufferers.

Cognition was 'rescued' in 7 male subjects aged between 20 and 50 years by administration of GnRH beneath the skin every 2 hours for 6 months in mimicry of physiological release from the hypothalamus onto the pituitary gland. It was found that the reproductive hormonal profile did not change, metabolic parameters were somewhat improved, cognitive performance increased in six, 'driven by sub-scores for visualisation function, executive function and attention, and a trend for episodic memory' in association with 'enhanced verbal comprehension'. Functional MRI studies revealed 'increased' connectivity in visual and sensori-motor regions and a return towards normal in the hippocampal system'.

The Lille summary.

The Lille researchers reported 'In our trisomic model...cognitive and olfactory deficits parallel a gradual loss of GnRH expression beginning in childhood and culminating in adulthood'.

However, 'Epigenetic, cellular, chemogenetic and pharmacological interventions that restore physiological GnRH abolish olfactory and cognitive defects in (trisomic) mice, whereas pulsatile GnRH therapy improves cognition and brain connectivity in adult (human) DS patients'.

They concluded 'GnRH plays a crucial role in olfaction and cognition, and pulsatile GnRH therapy holds promise to improve cognitive deficits in DS'.

They declared 'Our results provide the rationale to launch a randomised multicentre study to confirm the efficacy of pulsatile GnRH therapy in correcting the neurodevelopmental trajectory and age related decline seen in DS and other conditions such as Alzheimer's Disease that share similar molecular or functional underpinnings.'

What next?

Of course, I raised the possibility of Australian participation in that multi-centre trial and wondered about the possibility of replacing GnRH in the first months of life, to mimic the 'mini-puberty' and seek better brain growth and development from as early as possible. Why wait?

Regrettably, technical limitations would appear prohibitive for babies: it would be difficult to maintain a tiny tube beneath skin in which small amounts of GnRH would need to be pumped from a little pump

fixed on the surface. And anaemia-producing volumes of blood would need to be taken from the baby for analysis of effect which, in any case, is able only to be assessed indirectly by the amount of FSH and LH induced by the tiny concentrations of GnRH in peripheral blood. Indeed the normal range of circulating concentrations of GnRH is not fully established and, thus, insufficient replacement would be likely to perpetuate under-development while replacement in excess might actually lead, by itself, to a kind of Alzheimer's degeneration.¹⁵ Thus, much work needs to be done, but the history of medicine is an encouraging saga of unexpected advances. However, there would appear to be no reason to delay assessment of replacement of GnRH in older people with DS.

Important precedents.

The postulations from Lille that GnRH exerts a non-reproductive role in neuro-development are not new. Since elucidation, reports have emerged from experiments on cells in laboratory dishes, on brains of rodents and sheep, and from clinical experience with humans.

In the laboratory, it was demonstrated that neuronal cells exposed to blockers do not extend appropriate communicating branches and thus synapses with other cells are impaired¹⁶. Conversely, in another centre, it was demonstrated that GnRH 'increases both outgrowth number and length of neurites in cultured cerebral cortical neurons of rat embryos...suggesting... that besides its pituitary functions, GnRH may play a role as neuromodulator of neuronal plasticity'¹⁷.

Under the microscope, it has been revealed that women, administered blockers to reduce the role of oestrogen in endometriosis, have a marked reduction in the number of neurons in the walls of the intestine as revealed in biopsies performed to assess an associated, inordinate prevalence of intestinal symptoms¹⁸.

In the field, a number of studies have emanated from the veterinary school in the University of Glasgow where 'blockers' were administered to peri-pubertal sheep¹⁹²⁰²¹²²²³²⁴. In summary, it was found that 'blockers' resulted in pathological hypertrophy (enlargement) of the limbic system in the brain associated, at molecular level, with altered functions of multiple genes many of which were involved in the integrity of that structure which is basic to integration of memory, emotion (including sexual) and cognition, and then translation of these forces into executive function which may be defined as 'a set of skills...that... underlie the capacity to plan ahead and meet goals, display self-control, follow multiple-step directions even when interrupted, and stay focused despite distractions, among others'. In consequence, it was found that 'blocked' sheep suffered from reduced spatial memory (they could not decide which way to go in a known maze), increased emotional lability (they were unduly upset when separated from their peers), and a preference for the familiar over the novel (they were fearful of change). Moreover, the effect was sustained..

In cages, 'blocked' rodents have suffered 'profound effects' in behaviour associated with altered 'neural activity' in the limbic system. These effects range from depression, to hyperlocomotion (presumably based on anxiety), feeding disorder, preference for the familiar rather than exploration of the novel (that is fearfulness of change) and social disorder²⁵.

Under MRI imaging, it was found in an adolescent, natal boy administered 'blockers' (to pursue a female identity), that expected structural development of the brain did not occur and was associated with reduction in IQ²⁶. In another MRI study of otherwise healthy women, it was found blockers interfered with neuronal connectivity in the limbic region and were associated with the 'emergence of depressive symptoms'²⁷.

Perhaps of greatest importance, however, are the major abnormalities in the brain revealed in MRI in the rare Kallman Syndrome in which for a variety of genetic reasons the GnRH cells and the olfactory cells that arose together in the nasal placode on the face of the embryo have been unsuccessful in their intended journey into the brain. The results of this rare complication are reduction in the ability to smell because of interruption to nerves involved in the sensation of smell, and failure to enter puberty because of interruption to the cells producing GnRH. Though a variety of structural abnormalities in parts of the body have been described, major interruptions in the development of the brain have been reported. According to Manara et al 'Even though further validation is warranted, curvature, sulcation, cortical thickness, gray/white matter volume, and bone changes in patients with KS point toward a profound structural and morphologic involvement of the basal forebrain that is far more consistent than a simple hypoplasia of the olfactory sulcus'²⁸. Given the variety of genetic forces that guide the voyage of the cells into the brain, an overall genetic cause could be offered for all the abnormalities, rather than a specific lack of GnRH in brain development. Given, however, the consistency of the brain abnormalities, it is more logical to point to the particular lack of GnRH. More studies are needed, but, surely, the evidence of KS alone should reduce confidence in the blithe assurance that 'puberty blockers are safe and entirely reversible'...and this review appeared in 2014.

In men with prostate cancer receiving blockers to reduce production of testosterone, changes in mood and cognition have been reported²⁹³⁰. Similarly, predisposition to depression and reduction in working memory and executive function have been found in adult women, administered blocker to reduce production of oestrogen.³¹³²³³ In children treated with blockers to retard the development of precious puberty, the Lille researchers declare there has been a suggestion of reduction in IQ, but the numbers treated are small. And, assessment of the psychological effect of blockers in these cases is confounded by the reduction in stress associated with relief from the original condition.³⁴³⁵³⁶

Similarly, reports from gender clinics of improved psychological parameters in children being hormonally affirmed to a gender incongruent with chromosomes are confounded by the impact of publicity and applause from authoritative powers in the child's life: from a supporting parent, friends on the web, school teachers, the team of social and other medical workers in associated with gender clinics and, in some cases, the imprimatur of religious authorities. It should not be forgotten that, on the whole, the confusion over gender was associated with co-morbid psychological ill health and social disorder, often presenting with loneliness, anxiety and depression, all symptoms that can be expected to improve with concerted attention from caring adults.

Further explanation.

The effect of 'blockers' on the limbic system should not be under-estimated. As described, that part of the brain coordinates cognition, emotion, memory and desire into 'executive function'. It is biologically implausible, therefore, to proclaim that 'blocking' puberty permits time for mature consideration of gender and the mechanism and results of its hormonal and surgical re-orientation to a gender incongruent with chromosomes. The Lille workers have demonstrated the role of insufficient GnRH in overall brain function. The Glasgow workers have demonstrated a specific role in the integrating system and decision making part of the brain. It is implausible to argue that the child can make a responsible decision when neutered, not only from hormones, but from the appropriate capacity to evaluate information and act accordingly, especially given the natural immaturity of the disciplinary pre-central cortex that persists into the 20's. After all, common sense precludes children under 18 from even obtaining a life-lasting tattoo. Yet, gender clinics declare much younger children are capable of providing consent to incomparably greater medical

intervention despite their natural immaturity, their mental co-morbidity, the effect of blockers on cognition, and their effect on the limbic system.

Also, rodent and ovine studies that reveal a preference for the 'familiar over the novel' should not be under-estimated. Perhaps due to undue fearfulness associated with limbic disruption, the animal studies provide biological explanation for the observed fact that almost all children who are administered 'blockers' proceed with to the next stage of 'affirmation' to a gender incongruent with chromosomes: the administration of cross sex hormones.

Most likely, the phase of receiving blockers on the escalator of 'affirmation' has been preceded by a period of 'social affirmation' which has involved the giving of new names, new clothing, new status, sustained support from authority figures, 'cheer leading' status at school and even appearances on the media: all comprising the 'familiar' identification with the chosen gender. 'Novelty' would comprise rejection of all those influences and the adoption of the 'new gender'. Not only would there be enormous psychological challenges to undertake that change: a molecularly altered limbic appears likely to contribute to prohibitive fearfulness.

Lastly, while this review has concentrated on the effect of blocking GnRH, the effects on the brain of the next stage of 'affirmation' the administration of cross-sex hormones, should also not be underestimated. Two independent studies based on MRI imaging have revealed the male brain shrinks at a rate multiples faster than in ageing, after only a short period of administration of oestrogen in the process of transgenering. It is presumed brain cells 'apoptose' which is a euphemistic term for 'die'³⁷³⁸ Receiving testosterone in the process of transgenering, the female brain hypertrophies, that is, swells, for reasons unknown apart from the fact that there is no increase in neurons³⁹. Remember, the limbic systems in brains of sheep on 'blockers' hypertrophied (became pathologically enlarged) in association with much genetic disruption: No such studies have yet been performed on sheep administered cross sex hormones, let alone on humans. Yet the structural effects of hormonal interruption to the brain may prove to be an iatrogenic cause for the propensity of adult transgendered people to commit suicide at a rate far greater than the general population⁴⁰⁴¹⁴².

Proponents for transgenering declare the suicides reflect the impact of societal transphobia, declining to recognise the possibility that victims may have ended their lives because they had found no 'gold' at the end of the rainbow, or suffered from iatrogenic drug administration.

Conclusion.

Given the non-reproductive, neurological role of GnRH has been discussed for decades and is based on studies from many centres throughout the world, is it odd the only people who appear to be, at best, unaware of its implications are practitioners in gender clinics for children who blithely seek to assure, from Tavistok to Melbourne, that 'blockers are safe and entirely reversible' and continue to administer them to vulnerable children. Does this represent an inability to pursue literature relevant to their speciality? Or does it represent the power of what can only be understood as ideology? After all, there is much more warning about the side effects of blockers than there ever was over the side effects of thalidomide on developing babies.

I suppose one can't expect too much from legislators unfamiliar with biology, but how can it be explained that Mr Andrews' government in Victoria passed (with Liberal support) a Change and Suppression Act⁴³ that has criminalised any attempt, including traditional psychotherapy, to lead a gender confused child to come to terms with his or her chromosomes and to accept a scientifically allotted designation, thus avoiding even cerebral interruption from hormones, not to mention

ultimate surgical re-structuring of genitalia, including castration. There is something absurd in the Victorian parliament: up to 10 years in gaol for not insisting a nine year old confused over gender must pursue a pathway that leads to administration of hormones that will alter the brain and to surgery that is likely to remove the genitals.

And, is it not odd that institutions incorporating gender clinics appear unaware of the mandate of the Australian High Court in *Re Rogers vs Whittaker*⁴⁴ that medical practitioners are bound to inform recipients of interventions of the possibility of side effects which might occur only once in 12,000 instances? All of Glasgow's sheep were damaged by blockers! All of Lille's mice improved on GnRH, as did 6 out of 7 adult sufferers of Down Syndrome. Given the number of de-transitioners now regretting their interventions, the continued denial of non-reproductive side effects of blockers, and silence on the effect of cross-sex hormones on the brain, a legal bonanza is anticipated.

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