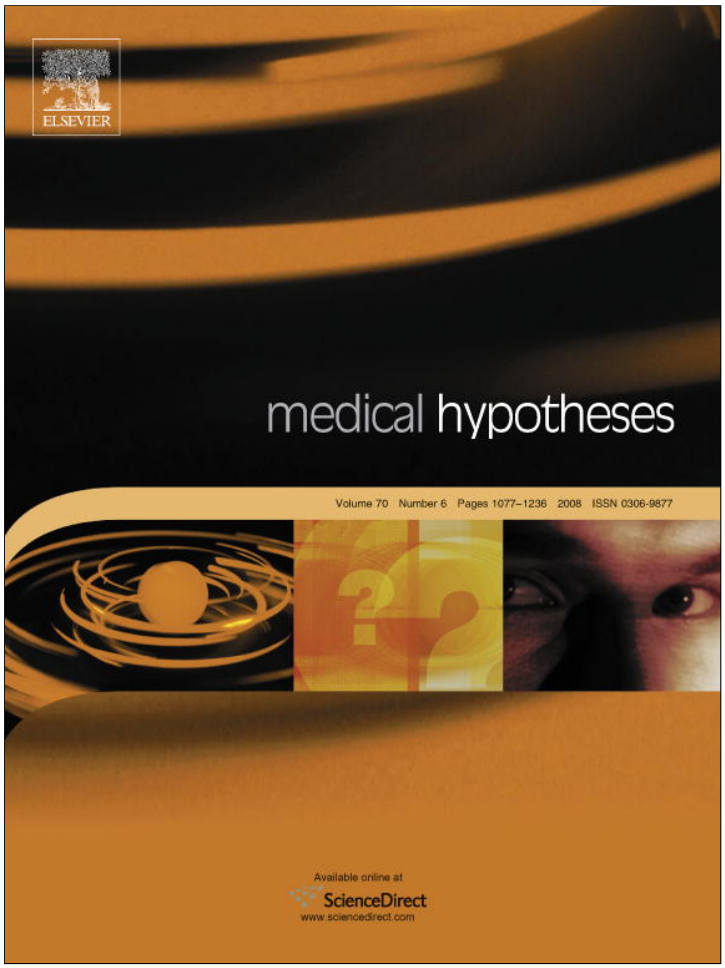

in AD-affected brain regions is still a matter of discussion.

We imagine that, in a ''rarefied'' neuronal network, occurring invariably during aging, exosomes could be the key player of neuronal communication. In this contest, exosomes could easily become the Trojan horses of neurodegeneration: a wide kind of factors (genetic or environmental) could decide — changing exosomes sorting and/or composition — the fate of those aging neurons forced to use this nano-compartment for their reciprocal communication. This hypothesis could explain why AD presents late during lifetime. The mechanism underlying the death of cells could be the shipping of toxic agents by Trojan exosomes. We draw a picture in which neurodegeneration in AD is triggered by proteins spread, cell by cell, throughout brain areas: the fact that these ''infected'' shuttles probably monopolize the intercellular traffic burst a massive neurodegeneration.In our opinion, this hypothesis has important implications for the fight against AD and other late onset neurodegenerative diseases.

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The vanishing follicle in women aged over forty: Premature, mechanical, LH-independent luteinization may reflect oocyte—follicle low quality?

Healthy ovulation in a natural cycle is triggered by a sharp rise in LH (LH surge). In ART cycle, hCG is used as an LH-surrogate. In order to prevent premature LH surge (and cycle cancellation), GnRH analogs (agonists or antagonists) are used. Indeed, LH surge is reliably prevented, setting the ground for precise ovulation timing with hCG. However, clinical experience indicates that premature luteinization does occur, even when frequent LH measurements rule out an endogenous LH surge. The population mostly affected by this phenomenon is patients in their 40s. A typical scenario is of a 40+ year old patient with 2—3 mature follicles (>17 mm in diameter), and compatible hormonal profile (normal LH levels), who is given a bolus of hCG as trigger the same day. However, on day of oocyte retrieval, some, or all of the follicles disappear, with concomitant appearance of free fluid in the Douglas pouch. Detailed review of hormonal records and patient compliance typically yields no apparent mistakes. Alternatively, during oocyte pick-up, a follicle bursts due to a moderate pressure on the abdominal wall in an effort to bring the ovary closer to the ultrasound transducer.

To the best of my knowledge, ''vanishing follicles'' have not been described in the medical literature; therefore, the mechanism remains speculative. It is well established that oocyte quality deteriorates with age, especially as a woman enters her fifth decade of life. It would seem surprising that other components of the follicular—oocyte unit would retain their young age quality. More likely, granulosa and theca cell layers, show signs of ageing in parallel to diminished oocyte quality. For the basement membrane, ageing may manifest as yielding to surrounding tissue pressure as the follicle grows, resulting in mechanical, LH or hCG-independent rupture of the follicle. Such rupture leads to follicular partial luteinization, and of course, will not produce a

fertilizable oocyte. Clinically, the growing follicles disappear without apparent rise in endogenous LH, while progesterone levels increase, albeit not to the same degree as expected following healthy luteinization. In the following cycle, it would seem wise to trigger ovulation before the follicles reach their spontaneous rupture diameter, though, based on personal experience, the chance for healthy pregnancy is very low.

In summary, patients over 40 years of age represent about 25% of ART activity in many centers. The ''vanishing follicles'' phenomenon is not rare in that population, probably reflecting diminished quality and ageing of the growing follicles.

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The potential utility of acetaminophen in the treatment of cell-mediated autoimmune disorders

It is shown that depletion of glutathione from antigen presenting cells *in vivo* results in lowered Th1 activity and higher Th2 activity, and GSH repletion has just the opposite effect [1].

Macrophage migration inhibitory factor (MIF) is a cytokine secreted by anterior pituitary and also by a variety of cells — primarily T cells and macrophages [2]. It is a potent activator of macrophages *in vivo* and stimulates T cell activation and proliferation and the secretion of the major type 1 cytokines. As MIF exerts anti-apoptotic effects, it may play a role in promoting abnormal survival of autoreactive lymphocytes, thereby perpetuating autoimmune reactivity. Moreover, glucocorticosteroids stimulate the secretion of MIF by immunocytes, and, interestingly, MIF counter-regulates the immunosuppressive effects of glucocorticoids [3].

Increased MIF plasma or serum levels were identified in patients with Crohn's disease, rheumatoid arthritis (RA), and multiple sclerosis. In addition, elevated levels of MIF were found within affected human tissues in immunoinflammatory disorders such as glomerulonephritis and psoriasis [4]. MIF may play a role in some Th2 disorders such as asthma as well, but in view of its promotion of Th1 activity, its role in fostering the type 1 autoimmune response seems more pronounced.

It is shown that treatment of mice with a subtoxic overdose of acetaminophen results in massive depletion of GSH [5]. Moreover, NAPQI, one of the acetaminophen's metabolites, is very effective in inhibition of MIF activities and significantly inhibits the ability of MIF to override the immunosuppresive effects of dexamethasone on LPS-induced TNF-α production by human monocytes [6].

Given that high cellular GSH levels and MIF promote the development of type 1 immune response and that acetaminophen metabolites deplete cellular GSH and inhibit MIF activity, acetaminophen may prove to be a novel treatment for type 1 autoimmune disorders. As glucocorticoid activity is kept in check by MIF, acetaminophen could therefore potentiate the anti-inflammatory actions of glucocorticoids and hence exert steroid-sparing effect. The maximum tolerated dose of acetaminophen has recently been reported to be 15 g/m^2 [7]. This is equivalent to 400 mg/kg [5].

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