lerates, and the menopause occurs when the number of primordial follicles has fallen to a critical number.[28 29]

The accelerated loss of primordial follicles in the perimenopausal phase occurs in parallel with rising gonadotrophin concentrations. It is not known, however, whether the rate at which ovarian follicular reserve becomes depleted is regulated primarily by factors within the ovary itself or whether the accelerated follicular loss at this stage results from a primary change in the control of gonadotrophins. Nor is the trigger mechanism known, nor what determines the timing of any altered neuroendocrine activity, particularly in the perimenopausal phase. Clearly the timing of the phase of accelerated follicular loss and its speed will determine age at onset of the menopause. Is the date of the menopause genetically "programmed" for each woman or might it be influenced through the neuroendocrine control of gonadotrophin secretion? Could the time at which menopause occurs be altered—forwards or backwards?

Factors such as parity, nutrition, race, and smoking influence the age at the menopause by at most three years either side of the normal median age. Some women, however, have a premature menopause—before the age of 40; in a few it occurs below the age of 30. Premature ovarian failure is probably much commoner than generally appreciated. In a series of 1001 women under the age of 40 presenting consecutively with amenorrhoea at an endocrine clinic 8% had never menstruated (primary amenorrhoea) (J Ginsburg *et al*, fifth international congress on the menopause, 1987). Of the remainder—that is, those with secondary amenorrhoea—9% had raised gonadotrophin concentrations and were considered to have premature ovarian failure. Seven per cent of this group had plentiful primordial follicles on ovarian biopsy, which suggests resistance to gonadotrophins—the resistant ovary syndrome. No ovarian follicles were found at laparoscopy in the remaining 93%. The cause of premature ovarian failure in the women without ovarian follicles was iatrogenic—the result of chemotherapy or radiotherapy—in 12% and autoimmune failure in 3%. But in most of those with premature ovarian failure no cause could be found for the absence of ovarian follicles.

In women with premature ovarian failure it is not clear whether fewer primordial germ cells migrate to the germinal ridge in fetal life, whether the rate of multiplication up to the fifth month of intrauterine life is reduced, whether the rate of follicular loss thereafter is greater than normal, or whether there is a combination of all three factors.

Almost all the factors reported to influence the age at the menopause accelerate its onset. Yet if we knew what determined follicular atresia and its accelerated onset in the perimenopausal phase could the process possibly be delayed and the potential store of viable primordial follicles be increased so that the menopause was delayed? Or is the limit set by natural aging processes in the reproductive system as a whole? Either way, knowledge of these factors and how they are integrated could have important implications for both regulating fertility and treating infertility.

JEAN GINSBURG

Consultant Endocrinologist,
Royal Free Hospital,
London NW3 2QG

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Physiological importance of nitric oxide

An endogenous nitrovasodilator

Since 1867 doctors have prescribed, unwittingly, a class of drug that mimics one of the body's own chemical messengers. One hundred and twenty years after Brunton first gave amyl nitrite for the treatment of angina[1] it was found that nitric oxide, which is the active component of amyl nitrite, glyceryl trinitrate, and other nitrovasodilators,[2] is an endogenous mediator.[3-5] The discovery of the "endogenous nitrovasodilator"[3 5 6] has clear parallels with the discovery of the endogenous opiates (enkephalins and endorphins)[7] and, even more recently, with the identification of an endogenous digoxin.[8]

Nitric oxide is synthesised from L-arginine by the vascular endothelium and accounts for the biological activity of the vasodilator endothelium derived relaxing factor.[3-5] The process is stereospecific and can be inhibited by a variety of analogues of L-arginine, including N^G monomethyl-L-

arginine.[6 9 10] Once released, nitric oxide acts by stimulating guanylate cyclase[6 11]; its half life is in the order of a few seconds,[3 5] and in solution it decays rapidly to nitrite and nitrate.

Within the circulation the main actions of endothelium derived nitric oxide seem to be dilatation of blood vessels[5] and inhibition of platelet aggregation[12] and adhesion.[13] The endothelium acts as a signal transducer, sensing changes in intraluminal flow[14] or chemical milieu[3 5 10] and modifying the output of nitric oxide accordingly. In many arterial beds release of nitric oxide appears to be continuous, providing a basal dilator effect[9 10]; in these beds inhibition of synthesis of nitric oxide leads to vasoconstriction.[9 10]

There are strong hints that attenuation of the nitric oxide pathway occurs in certain cardiovascular diseases. Atheroma is associated with localised impairment of the release or effect of nitric oxide, and this tips the balance in favour of constriction and thrombosis.[15-17] Alternatively, inactivation of released nitric oxide might contribute to the vasospasm of subarachnoid haemorrhage[18] as haemoglobin in the tissues binds avidly to nitric oxide and prevents it from relaxing the smooth muscle.[19] Indirect evidence suggests that a deficiency of dilatation mediated by nitric oxide may be present in essential hypertension,[20 21] and, if generalised, this might contribute to the increased blood pressure.[9 10]

Excess production of nitric oxide by the vasculature might also lead to disease. Animal models of septic shock are accompanied by the expression of a second distinct nitric oxide synthase enzyme in endothelial cells[22] and in the smooth muscle itself.[23] The increased production of nitric oxide that occurs after the appearance of this enzyme in the blood vessel wall seems to contribute to the hypotension.[23 24] Whether induction of nitric oxide synthase also occurs in patients with sepsis is not known, but the raised concentrations of nitrate excreted during infection suggest increased synthesis of nitric oxide.[25] Interestingly, the expression of the inducible nitric oxide synthase is inhibited by corticosteroids,[22 23] and this may have therapeutic implications.

Recently it has become clear that tissues outside the blood vessel wall may also synthesise nitric oxide and that this simple "inorganic" gas has a widespread role as a chemical messenger between and within cells.[6 11] Human platelets[26] and neutrophils[27] synthesise nitric oxide, and within the platelets the nitric oxide acts as an intracellular messenger, regulating platelet function.[26] In other species macrophages activated by certain cytokines kill micro-organisms and tumour cells by synthesising and releasing nitric oxide.[28 29] Central[30] and peripheral[31 32] neurones release nitric oxide, which may act as a neurotransmitter. Mast cells,[33] hepatocytes and Kuppfer cells, adrenal cells,[34] and kidney epithelial cells[35] have all been reported to release nitric oxide.[6 7] In evolutionary terms nitric oxide is a highly preserved mediator and seems to be present in reptiles[36] and birds[37] as well as mammals.

Better understanding of the L-arginine-nitric oxide pathway has already given insight into the mechanisms of action of current treatment. Most veins produce little if any nitric oxide under resting conditions[38] and consequently are particularly sensitive to exogenous nitric oxide in the form of the nitrovasodilators. The same holds true for arteries with endothelial damage.[39] This increased response to nitric oxide seen in veins and certain diseased arteries, together with possible local actions on platelets,[12 13] offers an explanation of the efficacy of nitrovasodilators in angina.

Nitric oxide is a recent addition to the long list of local mediators. It is now important to establish its contribution to clinical pathophysiology. The challenge will be to manipulate the different nitric oxide systems selectively; if this can be done new treatments are bound to follow.

JOE COLLIER
Senior Lecturer
PATRICK VALLANCE
Wellcome Trust Fellow
Department of Pharmacology and Clinical Pharmacology,
St George's Hospital Medical School,
London SW17 ORE

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