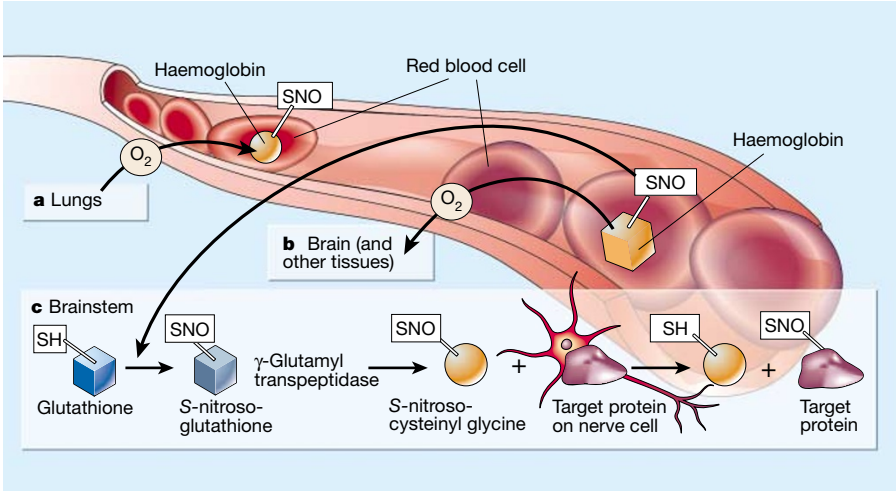

Figure 1 **How *S*-nitrosothiols (SNOs) work on the brainstem to control breathing.** a, **Haemoglobin is oxygenated in the lungs; one of its cysteine residues is then modified with SNO.** b, **Oxygen levels in the brain (and other peripheral tissues) are naturally low. Haemoglobin releases its oxygen and changes its shape in a way that ultimately promotes transfer of its NO group to another cysteine residue, in this case on glutathione** (c)**, by transnitrosylation. *S*-nitrosoglutathione is cleaved by the enzyme γ-glutamyl transpeptidase in neuronal tissue to form *S*-nitrosocysteinyl glycine. It is also possible that *S*-nitrosocysteinyl glycine is then cleaved by a peptidase to produce *S*-nitroso-L-cysteine. One of these two molecules is then proposed to transnitrosylate a cysteine residue in a target protein in the nucleus tractus solitarius region of the brainstem, regulating the central neuronal circuitry that controls breathing.**

In summary, the work of Lipton *et al.*[1] will make it into the physiology textbooks with four key observations. First, a blood-derived factor can control minute ventilation by acting on neurons in the nucleus tractus solitarius. Second, specific SNOs are involved. Third, enzymes (γ-glutamyl transpeptidase and possibly others) are needed to transfer the SNO signal from blood to brainstem. Finally, haemoglobin releases SNOs not only to produce local blood-vessel dilation — to match the oxygen requirements of different tissues to blood flow — but also to control areas in the central nervous system that are involved in breathing.

Given these results, we may legitimately question whether haemoglobin first evolved to carry oxygen or to ferry NO to key locations in the body. It has been argued that haemoglobin's original task was to enable reactions involving NO and SNOs to occur[5], and that its ability to carry oxygen came later; other work supports this view[6]. In fact, many responses to low oxygen levels (hypoxia) can be attributed to the SNO-generating transfer of NO groups from haemoglobin; these responses include those discussed above[1,3,4] as well as modulation of gene expression, which is mediated by increased activity of the transcription factor HIF-1 (ref. 7). Expression of these genes may also contribute, directly or indirectly, to hypoxic preconditioning — a mechanism whereby short exposures to hypoxia or ischaemia (lack of blood flow) can protect the heart and brain from damage resulting from more prolonged hypoxia[8].

The idea that the respiratory response to hypoxia is controlled by SNOs is radical, not only because NO was once thought to be inactivated by haemoglobin, but also because oxygen has always been viewed as central to cellular respiration and energy production. Nonetheless, it seems clear that NO-related molecules produce a web of control over the level, delivery and metabolism of oxygen. Oxygen works in concert with, and under the control of, SNOs.

How exactly do SNOs reach the brainstem from the blood? It seems likely that the mechanism involves transnitrosylation — the transfer of SNOs from a key cysteine residue of one peptide to another. A series of such reactions is apparently required to transfer the NO group from haemoglobin, first to the red-blood-cell membrane (probably through anion-exchange protein-1)[4], then onto glutathione in the blood and into endothelial cells (which line the walls of blood vessels)[9], and finally generating *S*-nitrosoglutathione in the brainstem (Fig. 1).

The process then requires γ-glutamyl transpeptidase to produce *S*-nitrosocysteinyl glycine, which might likewise be processed to form *S*-nitroso-L-cysteine, a molecule that has long been known to act in a stereospecific manner to reduce heart rate and blood pressure when injected into the nucleus tractus solitarius[10,11]. One interpretation of this stereospecificity is that there is a receptor for L- (but not D-) SNOs on brainstem neurons. Another is that a transporter molecule is involved in importing *S*-nitroso-L-cysteine or *S*-nitrosocysteinyl glycine into neurons. But it is equally

100 YEARS AGO

It has long been recognised that a change of surroundings may profoundly influence the reproductive system, in some cases increasing the fertility, in others leading to complete sterility… An Arab-Kattiawar pony which arrived during April from India proved during the first three months quite sterile, owing, I believe, to loss of vigour on the part of the germ-cells, their vitality being only about one-tenth that of a home-bred hackney pony. But the fertility is apparently impaired by even comparatively slight changes of environment. Lions which breed freely in Dublin seem to be sterile in London, and I heard recently that when bulls are changed from one district to another in the north of Ireland complete sterility is sometimes the result… No one doubts that the bodily vigour is liable to be impaired by fevers and other diseases, by changes in the habitat, unsuitable food, rapid and unseasonable changes of temperature, and the like; hence it will not be surprising if further investigations prove that changes in the soma, beneficial as well as injurious, are reflected in the germ-cells, and thus indirectly induce variation.

From *Nature* 12 September 1901.

50 YEARS AGO

Early last year Sir Stanley Unwin reviewed in a pamphlet entitled "How Governments Treat Books", some of the obstacles which taxation policy offers today to the free flow of books from one country to another… Sir Stanley in this pamphlet, rightly emphasizing the value of books for the transmission not merely of knowledge but also of thought, pointed out that post-war governments are treating with scant respect this unique and priceless instrument for giving continuity and permanence to the free expression of thought. In many otherwise civilized countries, there is an increasing tendency to treat books as if they were merely an ordinary commodity of commerce, without cultural value or importance. The fundamental principle that the one thing no country can afford to hamper, limit or tax is knowledge no longer receives the respect that it enjoyed a century ago; and in the climate of opinion that is engendered by security measures, once they escape beyond the limits that the national interest requires in such matters as atomic energy, the progress of knowledge is bound to slow down.

From *Nature* 15 September 1951.