decomposes rapidly into cysteine and NO[•]; the authors also suggested that some of the NO[•] generated from arginine at the haem iron of nitric oxide synthase may be carried to its receptors by thiols⁷⁻¹¹, but there is no convincing evidence for this¹².

The new results⁵ show that, in blood, NO[•] is bound to both the haem iron and the reactive sulphhydryl (SH) groups of cysteine 93β of haemoglobin. (In arterial blood [FeII NO] = 536±99 nM and [cysteine 93β SNO] = 311±55 nM. In venous blood [Fe NO] = 900±126 nM and [cysteine 93β SNO] is negligible). The concentration of haem iron in blood is about 9 mM, which makes the concentration of NO[•] carried by the blood about 1/10,000 of that of oxygen. NO[•] bound to haemoglobin in the absence of oxygen is relatively stable, but in its presence NO[•] is instantly converted to nitrate and the haem iron is oxidized to methaemoglobin which is then reduced by methaemoglobin reductase.

Reaction of NO[•] with the SH groups of cysteine 93β is controlled by the allosteric transition of haemoglobin and by the spin state of the haem iron: reactivity is high in the oxy or R-structure and low in the deoxy or T-structure¹³ and, within the R-structure, the off-rate of NO[•] is faster in high-spin methaemoglobin than in low-spin oxyhaemoglobin. Nature exploits this regulation. Liberation of oxygen in the tissues, accompanied by the allosteric transition from R to T, or by oxidation of the haem iron, causes NO[•] to be liberated by cysteine 93β and to be transferred to small thiols which may return it to endothelial receptors.

The authors proved their point by preincubating human erythrocytes with nitrosocysteine and then washing off all residual nitrosocysteine. The S-nitroso-oxyhaemoglobin thus produced in the erythrocytes transferred its NO[•] to small thiols which were exported to the endothelium. On the other hand, the authors report that treatment with dithionite, which removed the oxygen and converted haemoglobin to the T-structure, caused NO[•] to be transferred from the SH groups of cysteine 93β to the haem irons, but this seems unlikely because dithionite instantly destroys NO[•]. Incubation of oxy- or deoxyhaemoglobin with either SNO-glutathione or SNO-cysteine resulted in transfer of NO[•] to cysteine 93β, but in hardly any transfer of NO[•] to the haem irons.

By sequestering endothelial NO[•], solutions of free haemoglobin caused vasoconstriction both *in vitro* and *in vivo*. But when its SH groups were blocked with N-ethylmaleimide, the rise in tension was 20 per cent less; when the haem irons were oxidized and blocked with cyanide, it was 70 per cent less. This proved that both the haem irons and the SH groups act as NO[•] scavengers. Nitrosylation of the SH group inhibited the rise in vascular tension produced by free oxyhaemoglobins. Because

of its low affinity for NO[•], S-nitroso-methaemoglobin actually relaxed tension by release of NO[•]. In the presence of glutathione, S-nitroso-oxyhaemoglobin as well as S-nitrosomethaemoglobin relaxed tension, showing again that NO[•] is transferred to small thiols and then conveyed to NO[•]-receptors. *In vivo*, the methaemoglobin formed in the reaction of NO[•] with the haem iron of oxyhaemoglobin is instantly reduced to deoxyhaemoglobin by methaemoglobin reductase. On reduction of its haem irons, any NO[•] carried by its reactive cysteines would be liberated and could be transferred to small molecular thiols. These observations would explain why erythrocytes, which are rich in glutathione, cause no rise in vascular tension, whereas free haemoglobin dissolved in the plasma, which lacks glutathione, does raise tension. The biosynthetic pathway for the formation of nitrosothiols is not clear, because NO[•] does not nitrosylate thiol directly, but only in the presence of higher nitrogen oxides¹².

In the course of evolution of haemoglobin, only the haem-linked histidine and a phenylalanine which wedges the haem into its pocket have remained invariant; on the other hand, cysteine 93β has remained invariant in mammals and birds, which implies that it fulfils an essential function, but its nature has remained a mystery. The paper by Stamler and colleagues⁵ now suggests that it acts as an allosterically and iron-spin-controlled nitric oxide buffer, exchanging nitric oxide with low-molecular-weight thiols.

Several firms are engaged in clinical trials of genetically or chemically modified haemoglobins as blood substitutes. In phase I trials on healthy volunteers, infusion of a haemoglobin with covalently linked α-chains¹⁴ caused a transient rise in diastolic pressure of 10–12 mm Hg. This is not serious, but the authors suggest that it could be avoided by the addition of S-nitrosylated haemoglobin. This is an intriguing possibility. □

M. F. Perutz is at the MRC Laboratory of Molecular Biology, Hills Road, Cambridge CB2 2QH, UK.

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Grow your own

Why are addictive drugs illegal? Society cannot permit too many of its citizens to make themselves useless; but the true emotional reason is subtler. The addict seems to get pleasure directly. He doesn't have to work, or sell things, or jump through any approved social hoops to get it. He no longer needs society; he only needs his drug. This defiance of the rest of us is intolerable. He can't be allowed to get away with it.

The reality, of course, is different. The addict's pleasure gets ever feebler and briefer, and soon he is driven merely by the need to avoid pain — the agony of withdrawal. His drug is illegal; he has no approved way of getting it; so he turns to crime, thus compounding his own miseries and adding to everyone else's. There must be a better way.

In this connection, Daedalus recalls the hope and hype of gene therapy. A few living cells are taken from the patient's body; a new gene is inserted into them by standard methods; and they are then put back. Thereafter, they release into his body the biochemical expressed by the gene. With luck it cures his disease.

The major addictive drugs are, of course, made by genes — those of the opium poppy and the coca bush. Animal and plant genes are quite compatible; firefly genes continue to work inside tobacco plants, which then glow in the dark. So Daedalus hopes to isolate the genes for the main plant narcotics, and find ways of inserting them into human cells. When put back into the donor, the cells will leak a steady supply of the narcotic into his bloodstream. Brain cells, though hard to extract and replace, would be ideal. With such precise targeting, even tiny traces of drug, from very few implanted cells, would be effective.

With a secure supply of his drug inside him, the addict will be freed from his major problem. The pangs of withdrawal will no longer force him into crime. He will not even be able to sell his supply to other addicts. His implant will give him no sinful pleasure — that stage of his addiction passed long ago — but he will at least feel fairly normal. He should be able to shoulder the burdens of responsible citizenship once more.

Such a simple, permanent solution will not be popular. The pushers and drug barons will lose their profits, the addicts will lose their dramatic pose as defiant losers, the police and the drug-clinics will lose a rich field of activity, and the law-abiding citizens will lose the spectacle of wickedness meeting its just deserts. But, says Daedalus, never do by law what you can do by engineering, particularly if the law doesn't work. It seems worth a try.

David Jones