

## Say "NO" to Erectile Dysfunction

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Nitric oxide was discovered by Priestley in the year seventeen seventy-two.  
He described it as a colorless, odorless gas and noxious to animals too.  
Two elements, nitrogen and oxygen, link covalently in equal proportions to form  
Nitric oxide in the atmosphere when lightning strikes, as in a storm.

So, by no stretch of imagination was it possible to relate this compound  
To human biochemistry; its properties were too toxic for it to be found  
In the cocktail of innocuous biomolecules, which are found in a living cell;  
Where all reactions occur at the moderate temperature in which they dwell.

The story began with the proposition of an endothelium-derived relaxing factor.  
In the sequence of events it was considered to be a prime actor or a director.  
Its true nature could not be deciphered and so as EDRF it was known, until,  
Much to the surprise of most scientists, as nitric oxide it was shown.

When enzymes known as nitric oxide synthases act upon L-arginine  
As well as NADPH and oxygen, they form nitric oxide and citrulline.  
This is the biochemical basis for the production of this elusive metabolite.  
Thus, emerges NO from the dark tunnel, full of vigor, vitality, and might.

Within a matter of seconds, NO gains entry into smooth muscle cells.  
Upon the heme moiety of cellular guanylate cyclase, it briefly dwells.  
This activates the enzyme, which acts upon the substrate guanosine triphosphate,  
To produce the second messenger, called cyclic GMP, at a fast rate.

Specific protein kinases get activated, intracellular calcium levels fall.  
The dilatory effect of vascular smooth muscle results at the end of it all.  
However, the down-stream effects of NO last for a few seconds, to be precise.  
A specific 5-phosphodiesterase opens up cyclic GMP, bringing about its demise.

If someone were to dub NO as a jack of all trades, it would be rather unfair,  
As this amazing molecule executes complex functions at several sites with panache and flair.  
Among the multitude of roles that it performs is this one, which is undoubtedly unique.  
It initiates a cascade of events, which culminates in penile erection, so to speak.

It therefore stands to reason that it grabbed a lot of attention, once it was known  
That this molecule could provide the answers; an elixir that could be home grown.  
A perfect therapeutic target for erectile dysfunction that might be simple, safe, and just right.  
It was still a dark tunnel; but there was some hope that at the end there would be light.

Could the steady state concentration of cyclic GMP be maintained for a longer while?  
Could this enzyme 5-phosphodiesterase be rendered inactive with a guided missile?  
Scientists were intrigued with this possibility and searched for that perfect drug.  
Until they stumbled upon a molecule that fitted perfectly, like a socket and its plug.

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Phosphodiesterases are homodimeric; of two identical subunits they are formed.  
Each with a catalytic domain for cyclic GMP and with a regulatory domain is armed.  
An exogenous molecule called “sildenafil” was found to be a perfect match;  
It could enter with ease into the alien space and even secure itself with a latch.

Lo and behold, the wonderous effect that this seemingly simple interaction produces.  
Blood gushes into the corpus cavernosa with great force, and a penile erection it induces.  
What if the phosphodiesterase enzyme is fooled into holding onto a fake substrate?  
Cyclic GMP has been spared to act for a few seconds more and helped open the sluice gate.

The story of nitric oxide has crossed the boundaries of pure chemistry, that’s for sure.  
Taking giant strides, it has stepped into the realm of human physiology, as it seems to lure  
Medical scientists and pharmacologists, for whom this molecule seems like a treasure trove.  
If erectile dysfunction has an answer, there are possible many more fruits to pick in that grove.

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