Nitric oxide is a neurotransmitter found in the central and peripheral nervous systems. Nitric oxide synthase (NOS) is localized in the central nervous system, including the nucleus of the solitary tract, nucleus ambiguus and dorsal motor nucleus of the vagus. These are regions that are implicated in the central control of swallowing and esophageal motility. In rats and rabbits, NOS has been shown to be present in the nucleus subcentralis of the nucleus of the solitary tract, and is thought to be responsible for the central programming of the striated muscle component of esophageal peristalsis. Beyak and co-workers from the University of Toronto, Toronto, Ontario provided evidence that the L-arginine-nitric oxide pathway is implicated in the central control of swallowing and esophageal motility. They studied oropharyngeal swallowing as well as esophageal peristalsis, and determined the functional role of brain stem nitric oxide by examining the effects of blockade of central nervous system NOS on swallowing, and on primary and secondary peristalsis. Administering NOS inhibitors intravenously or intracerebroventricularly into the fourth ventricle produced a number of oropharyngeal swallows and induced primary peristalsis in the smooth muscle portion of the esophageal body. NOS reduced the number of oropharyngeal swallows and the incidence of primary peristalsis in both smooth and striated muscle, and reduced the amplitude of peristalsis and smooth muscle contraction. This suggests that nitric oxide is a functional neurotransmitter in the central pattern generator responsible for swallowing and the central control of esophageal peristalsis. Peripherally administered NOS inhibitor can access structures within the blood-brain barrier to affect neuronal activity and physiological function. The central pattern generated for swallowing and esophageal peristalsis is sug-
gested to be a serial network of linked neurons within the
nucleus of the solitary tract and neighbouring reticular for-
motion, and there is likely one subnetwork for the orophar-
yngeal phase and the other for the esophageal phase of
swallowing. The neurotransmitters mediating striated and
smooth muscle peristalsis may be both anatomically and
neurochemically distinct. The role of nitric oxide in the
pathogenesis of esophageal motility disorders remains to be
established.

Over the past 10 years, more than 30,000 papers on
nitric oxide have been published. Surprisingly, nitric oxide
may have a beneficial as well as a detrimental effect in, for
example, models of inflammation. There are numerous
forms of NOS, including the constitutive form (cNOS), the
neuronal form (nNOS) and the endothelial (eNOS) form,
as well as the inducible form (iNOS). Nitric oxide is syn-
thesized from a guanidine group of L-arginine and can be
produced by almost all mammalian cells. eNOS appears to
be a homeostatic regulator of numerous essential cardiovas-
cular functions. In the gastrointestinal tract, cNOS regu-
lates epithelial permeability. Inhibition of nitric oxide
causes many of the features of intestinal inflammation,
including increased neutrophil recruitment, increased
oxidative stress, mast cell degranulation, and increased
microvascular and epithelial permeability. In the trini-
trobenzene sulphonic acid (TNBS) model of colitis, inhibi-
tion of NOS by the oral administration of nonspecific
inhibitors in the intestine exposed to TNBS provides dra-
matic protection and restitution in seven days, yet chronic
NOS inhibition in the absence of TNBS causes intestinal
inflammation. In a timely review of iNOS, Kubes et al pro-
posed that the iNOS-producing cells need to be character-
zized to determine what role this inhibition may play in
health and disease. They suggested that the hypothesis that
“…cNOS is good and iNOS is bad is far too simplistic and
no longer explains the majority of data generated by the sci-
entific community”.

The etiology of the initiation and recurrence of inflam-
matory bowel disease is unknown, and a number of factors
have been proposed, including increased epithelial motility,
appropriate neutrophil infiltration, activation of mast
cells and increased concentrations of pro-inflammatory
mediator such as cytokines, leukotrienes and reactive oxy-
gen metabolites. Nitric oxide has also received attention as
an important player in the pathogenesis of inflammatory
bowel disease. Nitric oxide is a weak free radical that can
react with superoxide to produce peroxynitrite. McCafferty
et al elegantly reviewed the importance of peroxynitrite
and inflammatory bowel disease, and proposed that this
molecule may play an important role in the physiological
and pathophysiological processes contributing to inflamma-
tory bowel disease.

The hyperdynamic circulation seen in patients with cir-
rhosis may be due to increased vascular tone, whereas cir-
rhotic cardiomyopathy may be due to impaired cardiac
contractile responsiveness to stressful stimuli. The vasodila-
tor nitric oxide is thought to be a possible mediator of the
hyperdynamic circulation in cirrhosis, in which increased
levels of cytokines stimulate the activity of iNOS to pro-
duce excess amounts of nitric oxide. In noncirrhotic
humans and in animal models of heart failure, nitric oxide
is a negative inotropic and chronotropic agent. In bile duct-
ligated cirrhotic rats, cardiac tumour necrosis factor (TNF-α),
iNOS mRNA and protein, cGMP and interleukin-1 (IL-1)-β,
and nitrite/nitrate levels were higher than in controls (Liu
et al). The increased cytokinemia in cirrhosis may be due to
enteric bacterial translocation through the gut wall, result-
ing in portal venus bacteremia and endotoxemia. The well
known negative inotropic effects of TNF-α and IL-1β are
abrogated by N^G-nitro-L-arginine methyl ester administra-
tion, indicating that these effects are mediated by a nitric
oxide-dependent pathway, at least in the cirrhotic heart.
Nitric oxide inhibits beta-adrenergic receptor-stimulated
contractility via a cGMP-mediated inhibition of voltage-
dependent calcium ion current. The authors propose that
the increased nitric oxide production in this animal model
may play an important role in the pathogenesis of cirrhotic
cardiomyopathy.