GARLIC (Allium sativum, Liliaceae/Alliaceae) has long been used for medicinal and culinary purpose. Its first medicinal use was reported 400 years ago, and documented medicinal use can be found in a research finding of Louis Pasteur in the 1800s (8). Originally used as a digestive aid and as an antifungal, antibacterial, or antiviral compound (during the World Wars it achieved the nickname Russian penicillin), garlic was first reported to be a cardioprotective agent in the 1980s (13). Much of its cardioprotective abilities have been attributed toward its ability to function as an antioxidant (4). For example, garlic contains antioxidant vitamins A, C, and E as well as selenium, a key element for the synthesis of the antioxidant enzyme glutathione peroxidase (6).

The study by Chuah, Moore, and Zhu (3) appears to be the first report where an alternative mechanism of cardioprotection is proposed. This report is based on the fact that garlic contains an organosulfur-containing compound, S-allylcysteine (12). Raw garlic contains alk(en)yl cysteine sulfoxides and γ-glutamyl alk(en)yl cysteines, which upon activation, is converted into S-allylcysteine (deoxyallin) because of the deactivation of the enzyme allinase. Allicin is then formed from S-allyl-L-cysteine according to following scheme:

These compounds are completely broken down into several volatile compounds, including hydrogen sulfide (H2S), as shown below:

The long-held belief that allicin generated from alliin (inactive compound present in garlic) by the action of the enzyme allinase (activated when garlic is pressed or crushed) is responsible for various health benefits is challenged from the findings that allicin can be readily oxidized into over 75 sulfur-containing compounds such as S-allylcysteine, as reported in Ref. 3. In addition, garlic produces several other sulfur-containing substances, including ajoene methyl allyl sulfide, which possesses the ability to lower cholesterol (2).

Until recent years, H2S was considered a toxic gas, responsible for various health problems, including inhibition of cytochrome oxidase at the end of the mitochondrial respiratory chain (9). Most of the adverse effects of H2S intoxication are due to the action on the nervous system, including conjunctival irritation (at ~15 mg/m³ H2S) and respiratory irritation (at >400 mg/m³ H2S). At a very high concentration of >100 mg/m³, H2S may lead to convulsions, unconsciousness, and finally to death. It is generally believed that H2S may not affect the cardiomyocytes directly but depresses cardiac function because of the secondary anoxia. Only recently, this toxic neurotransmitter has been found to protect the heart from cellular injury. Again, the same group (3) must be credited for several seminal observations on the cardioprotective effects of H2S. Since the proposal that H2S might be the “third endogenous signaling gasotransmitter” (after NO and CO; see Ref. 14), several groups showed health benefits of this gaseous molecule. For example, H2S was shown to regulate myocardial contractile function (5). Based on the observation that H2S activated the ATP-dependent potassium channel (10), it was proposed that this compound could exert a preconditioning-like effect. The same group (3) demonstrated that H2S induced cardioprotection by preconditioning the rat heart and cardiac myocytes (11). Subsequent work by this group found that, similar to ischemic preconditioning, H2S also preconditions the heart through the phosphoinositide 3-kinase-protein kinase B pathway (7).

There is little doubt that H2S is able to exert a preconditioning-like effect. In the present manuscript (3), Chuah, Moore, and Zhu cleverly connected their recent findings (15) with the fact that S-allylcysteine present in garlic is the source of H2S. This seminal observation certainly deserves credit. In biological tissue, H2S is produced from L-cysteine by the action of cystathionine-β-synthase and cystathionine-γ-lyase (1), as shown below:

In heart, cystathionine-β-synthase does not play any significant role in generating H2S under normal conditions, but cystathionine-γ-lyase appears to be involved in the generation of H2S endogenously (15). In this study, the authors found a reduction in cystathionine-γ-lyase gene expression in the infarcted myocardium. This result is consistent with the existing reports that H2S supplied exogenously from

Address for reprint requests and other correspondence: D. K. Das, Cardiovascular Research Center, Univ. of Connecticut School of Medicine, Farmington, Connecticut

http://www.ajpheart.org
NaHS could precondition the myocardium against ischemia-reperfusion injury.

In summary, the results of the study reported by Chuah, Moore, and Zhu (3) in this issue suggest for the first time that S-allylcysteine can be used as a source of H$_2$S that can lead to cardioprotection. These results appear to have a far-reaching impact, as discussed in this editorial. Garlic may be used (as nutritional supplement) directly as a source of S-allylcysteine to form H$_2$S endogenously, which then can render the heart resistant to ischemic heart disease.

REFERENCES