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[54] **ENHANCEMENT OF EXERCISE PERFORMANCE BY AUGMENTING ENDOGENOUS NITRIC OXIDE PRODUCTION OR ACTIVITY**

[75] Inventors: **Andrew J. Maxwell**, Fremont; **John P. Cooke**, Palo Alto, both of Calif.

[73] Assignee: **The Board of Trustees of the Leland Stanford Junior University**, Stanford, Calif.

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[58] **Field of Search** 514/249, 458, 514/474, 556, 564, 565, 665, 625, 763; 424/702

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,026,721 6/1991 Dudrick et al. 514/396

FOREIGN PATENT DOCUMENTS

0 259 167 A2 3/1988 European Pat. Off. .
0 680 945 A2 1/1995 European Pat. Off. .
296 20 015
U1 2/1997 Germany .
197 20 818
A1 5/1998 Germany .

OTHER PUBLICATIONS

Wasserman, et al. "Principles of exercise testing and interpretation"; Chapter 3, pp. 52-61 (1994).
Niebauer, et al. "Chronic exercise training attenuates atherogenesis in hypercholesterolemia mice" (*Circulation* 1998).
Stein, et al. "The cardiac response to exercise training: echocardiographic analysis at rest and during exercise" (*Am J Cardiol* 1980; 46:219-225).
Frick, et al., "Cardiovascular dimensions and moderate physical training in young men" (*J Appl Physiol* 1970; 29:452-455).
Blomqvist, "Cardiovascular adaptations to physical training" (*Annual Review of Physiology* 1983; 45:169-89).
Nakashima, et al. "ApoE-deficient mice develop lesions of all phases of atherosclerosis throughout the arterial tree" (*Arteriosclerosis and Thrombosis* 1994; 14:133-140).
Paigen, et al. "Atherosclerosis susceptibility differences among progenitors of recombinant inbred strains of mice" (*Arteriosclerosis* 1990; 10:316-323).
Jayakody, et al. "Cholesterol feeding impairs endothelium-dependent relaxation in rabbit aorta" (*Canadian Journal of Pharmacology* 1985; 63:1206-1209).
Freiman, et al. "Atherosclerosis impairs endothelium-dependent vascular relaxation to acetylcholine and thrombin in primates" (*Circ Res* 1986; 58:783-9).

Musch, et al.: "Effects of high-intensity sprint training on skeletal muscle blood flow in rats" (*Journal of Applied Physiology* 1991; 71:1387-1395).

Heinegard, et al., "Determination of serum creatinine by a direct colorimetric method" (*Clin Chim Acta* 1973; 43:305).

Maxwell, et al., "Hypercholesterolemia impairs exercise capacity: Role of nitric oxide" (*American Journal of Physiology* 1998, submitted for publication).

Bode-Böger, et al., "L-arginine infusion decreases peripheral arterial resistance and inhibits platelet aggregation in healthy subjects" (*Clin Sci (Colch)*1994).

Bode-Böger, et al, "Exercise increases systemic nitric oxide production in men"*(*Journal of Cardiovascular Risk* 1994; 1:173-178).

Harpur, "The rat as a model for physical fitness" (*Comp. Biochem. Physiol.* 1980; 66A:553-574).

Beaver, et al., "A new method for detecting anaerobic threshold by gas exchange" (*J Appl Physiol* 1986; 60:2020-7).

Böger, et al., "Long-term administration of L-arginine, L-NAME, and the exogenous NO donor molsidomine modulates urinary nitrate and cGMP excretion in rats" (*Cardiovasc Res* 1994; 28:494-9).

Maxwell, et al., "Limb blood flow during exercise is dependent upon nitric oxide" (*Circulation* 1998, Accepted for publication).

Barclay, et al., "The role of blood flow in limiting maximal metabolic rate in muscle" (*Medicine and Science in Sports and Exercise* 1975; 7:116-119).

Schaible, et al., "Cardiac adaptations to chronic exercise" (*Progress in Cardiovascular Disease* 1985; 27:297-324).

Wasserman, "Coupling of external to cellular respiration during exercise: the wisdom of the body revisited" (*American Journal of Physiology* 1994; 266:E519-E539).

Caru, "Regional flow responses to exercise" (*Chest*, 101/5/ May 1992/Supplement).

Maxwell et al., "L-arginine enhances nitric oxide synthesis and aerobic exercise capacity," (draft for publication, Aug. 17, 1998).

Barbee, et al., "Microsphere and dilution techniques for the determination of blood flows and volumes in conscious mice" (*American Journal of Physiology* 1992; 263:R728-R733).

Derwent Publications Ltd. (Jun. 7, 1991) *Horse Breeding Res.* abstract.

CA 130:167597, Berg et al., 1998.

CA 128:326546, Burgstiner, May 1998.

CA 127:148637, Volek et al., 1997.

Primary Examiner—Kimberly Jordan
Attorney, Agent, or Firm—Bertram I. Rowland; Rae-Venter Law Group, P.C.

[57] **ABSTRACT**

NO precursors are administered at elevated levels in addition to the diet of the individual to enhance exercise performance. Particularly, L-arginine and L-lysine by enhancing endothelial NO production can provide for greater aerobic capacity and improved exercise performance.