CC/NUMBER 42
OCTOBER 15, 1984

This Week's Citation Classic™

Gavras H, Brunner H R, Turini G A, Kershaw G R, Tifft C P, Cuttelod S, Gavras I, Vukovich R A & McKinstry D N. Antihypertensive effect of the oral angiotensin converting-enzyme inhibitor SQ 14225 in man.
N. Engl. J. Med. **298**:991-5, 1978.
[Dept. Med. and Thorndike Res. Inst., Boston Univ. Med. Ctr., MA; Dept. Med., Hôp. Cantonal Universitaire, Lausanne, Switzerland; and Squibb Res. Inst., Princeton, NJ]

The antihypertensive effects of an inhibitor of the potent pressor hormone angiotensin II were described in patients with severe hypertension refractory to conventional medications. This study demonstrated the value of this novel therapeutic modality that has since become established treatment for hypertension and congestive heart failure. [The *SCI*® indicates that this paper has been cited in over 440 publications since 1978.]

Haralambos Gavras
Department of Medicine
Boston University School of Medicine
Boston, MA 02118

June 29, 1984

"The contribution of the renin-angiotensin system in the development and maintenance of high blood pressure had been a matter of controversy despite extensive investigation for many years. While studying a Brazilian snake venom extract, Ferreira[1] discovered a number of polypeptides that, among other actions, could inhibit the formation of angiotensin II and that were shown by Krieger *et al.*[2] to have an important antihypertensive effect in animals. I had been interested for many years in the role of angiotensin in hypertension and cardiac function. When a derivative of these snake venom extracts was synthesized at Squibb[3] and purified for human use, I saw the opportunity to test my theories regarding the relationship of renin and sodium in blood pressure maintenance in man.

"This work was an example of how intensive research in the pathophysiology of hypertension over several years finally culminated in the development of a new potentially lifesaving therapeutic concept. A parallel study describing for the first time the use of angiotensin blockade in congestive heart failure was first greeted with skepticism and, in fact, was rejected by several British and American journals before it was accepted by *Circulation*.[4] Both papers were followed by a flurry of clinical research activity by investigators in several countries, which eventually established the advantages of this approach in the treatment of both hypertension and congestive heart failure. Three years later, the compound (Captopril) received FDA approval and has since come into increasingly wide use as treatment for these conditions.[5,6] Furthermore, a number of second-generation converting-enzyme inhibitors have been developed and tested since then for possibly higher potency, longer duration of action, and fewer adverse reactions. I believe the wide practical applications and the large number of clinical studies spurred by the original observations described in our paper are the reasons that this paper has become a *Citation Classic*."

1. **Ferreira S H.** A bradykinin-potentiating factor (BPF) present in the venom of *Bothrops jararaca*. *Brit. J. Pharmacol.* 24:163-9, 1965. (Cited 175 times.)
2. **Krieger E M, Salgado H C, Assan C J, Greene L L J & Ferreira S H.** Potential screening test for detection of overactivity of renin-angiotensin system. *Lancet* 1:269-71, 1971. (Cited 110 times.)
3. **Ondetti M A, Rubin B & Cushman D W.** Design of specific inhibitors of angiotensin converting enzyme: new class of orally active antihypertensive agents. *Science* 196:441-4, 1977. (Cited 530 times.)
4. **Gavras H, Faxon D P, Berkoben J, Brunner H R & Ryan T J.** Angiotensin converting enzyme inhibition in patients with congestive heart failure. *Circulation* 58:770-6, 1978. (Cited 105 times.)
5. **Gavras H, Brunner H R & Gavras I.** Captopril in the treatment of hypertension. *Ann. Intern. Med.* 95:505-6, 1981.
6. **Gavras H.** Hypertension and congestive heart failure: benefits of converting enzyme inhibition (Captopril). *J. Amer. Coll. Cardiol.* 1:518-20, 1983.

