cessful use in asthma was as a "vasoconstrictor". You can say that the early workers did the right thing (discovering the antiasthma efficacy of adrenaline) for the wrong reason (vasoconstriction). Indeed, the alleged mechanisms of action must still frequently be questioned, altered, or remain unknown when interesting *in vivo* effects of experimental compounds are being observed[3]. After adrenaline came more selective agents. Several years before the introduction of α- and β-receptors, the particular properties of isoprenaline (a bronchodilator without vasoconstrictor effects) were described, and well before the proposal of β_1- and β_2-receptors the bronchoselective drugs terbutaline and salbutamol were produced[3]. In these cases the 'basic research' (α-, β-, β_1-, and β_2-receptors) has not preceded but rather been dependent on the drug discoveries.

In 1900 Solomon Solis–Cohen[4] described the antiasthma effect of maintenance therapy with dried bovine adrenals ingested in amounts of 2–6 g daily: "The constant dyspnea first disappeared, the paroxysmal nocturnal attacks became less frequent and less severe. Recovery was not rapid but was continuous." Solis–Cohen's erudite essay, frequently mistaken for the first report on adrenaline efficacy, is probably the original demonstration of steroid drug efficacy in asthma[3]. Seventy to 80 years later inhaled steroids were developed through clinical and animal research with a focus on airway-lung selectivity *in vivo*. Such heuristic discoveries agree with that used in the development of novel β-agonists. Thus, it is a mixture of basic and goal-oriented research in which new, sometimes unexpected, observations in complex biosystems lead to novel drugs.

Breakthrough observations of "off-label" actions of molecules can obviously be used to develop innovative drugs before the acknowledged theoretic research has been able to predict such possibilities. *In vivo* test systems harbouring complex features of diseases will in all likelihood continue to be fertile fields where exploration-minded *in vivo* scientists can make original and important observations. Yet, this research has been and is increasingly "dismissed as being phenomenologic and of little scientific interest"[1].

CARL PERSSON
Department of Clinical Pharmacology
Lund University Hospital
S-221 85 Lund, Sweden

To the editor — Wurtman and Bettiker, in an otherwise excellent Commentary[1], point out that the search for significant new medical agents in the last thirty years was less productive than in the preceding thirty years. However, the authors err in projecting that this drug lag will continue. They state that "Treatment discovery turns out to be very much a directed or mission-orientated enterprise . . . ." This is a misreading of history. Major medical breakthroughs have come from investigator-originated research. This basic research, with a blossoming of studies on the human genome and on methods of isolating, characterizing and synthesizing macromolecules like nucleotides and proteins, has brought us to the brink of the greatest wave of drug discovery, both qualitatively and quantitatively, in history.

How can one escape the conclusion that the identification of hundreds (and soon thousands) of DNA sequences that are associated with clinical disease will lead to important progress in diagnosis and treatment. Similarly, on the protein front, hundreds of proteins are being identified as correlating with genetic anomalies. Methods of protein characterization such as laser desorption and electrospray mass spectrometry, are being used to identify proteins localized on two-dimensional gels, and to correlate these with specific genes. Each one of these becomes a clue to drug discovery. How can one help but conclude that a cornucopia of drug discovery is spilling forth, even as we speak?

MAXWELL GORDON
AJI Pharma USA, Inc.
Glenpointe Centre West
500 Frank W. Burr Boulevard
Teaneck, New Jersey 07666, USA

Wurtman & Bettiker reply — We appreciate Dr. Gordon's comments and salute his optimism that the fruits of investigator-initiated basic-science research now place us at the "brink of the greatest wave in drug discovery history."

Similar expectations articulated two decades ago — that the discovery of brain peptides would soon lead to new types of drugs, including addiction-free opiates — or one decade ago — that monoclonal antibodies would soon constitute cures for septic shock, various cancers and graft-versus-host disease — remain unfulfilled, and the historical record clearly fails to support Gordon's assumption that the discovery or production of "new" biomolecules, *per se*, leads to their use in treating disease. When 'new' endogenous compounds have become useful drugs (for example, with the interferons and interleukins) it has almost always been because clinical investigators discovered off-label uses for them. If one is inclined to disagree with this reading of history, examples should be cited.

Perhaps this decade's biomolecules will contribute more to therapeutics than the brain peptides or monoclonal antibodies of the past. We hope so. But in order for this to occur, we must increase our investment in the approaches that make new drugs out of such chemicals by increasing the pool of well-supported clinical investigators and systems physiologists, as well as by underwriting clinical studies on new uses for existing compounds.

It should also be recognized that the Human Genome Project is a prime example of mission-oriented research. Individual molecular biologists work toward a common goal, utilizing agreed-upon methods and criteria for success — just like the Manhattan Project.

RICHARD J. WURTMAN &
ROBERT L. BETTIKER
Department of Brain and Cognitive Sciences
Room E25-604
Cambridge, Massachusetts 02142-1323, USA

1. Wurtman, R.J. & Bettiker, R.I. The slowing of treatment, 1965–1995. *Nature Med.* **1**, 1122–1125 (1995).
2. Salter, H.H. *On asthma: Its pathology and treatment*, 2nd edn. (Churchill, London, 1868).
3. Persson, C.G.A. *In vivo* veritas. *Thorax* (in the press).
4. Solis–Cohen, S. The use of adrenal substance in the treatment of asthma. *JAMA* **34**, 1164–1166 (1900).