Hypertension gives no warning signs. Left untreated, it can lead to kidney and heart disease, retinal damage, and stroke. Its root causes are mostly unknown. About 190 million people in developed countries suffer from hypertension. The American Heart Association estimates nearly one in three U.S. adults have suffered from hypertension. The American people in developed countries are mostly unknown. About 190 million people in developed countries have high blood pressure and that over a third of them do not effectively control it.

One of the key regulators of blood pressure is the renin angiotensin system (RAS). The RAS cascade is initiated by renin, a protease produced by the kidneys that cleaves the peptide angiotensinogen, converting it to angiotensin I. Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE), which spurs blood vessels to contract and increases vascular resistance, raising blood pressure. Blocking either the formation or the action of angiotensin II is considered to be an effective way to control hypertension.

The existence of the renin pathway was first theorized in 1898 by Robert Trierstedt, a physiologist at the Karolinska Institute who experimented on rabbit kidneys. Renin catalyzes the rate-limiting (or bottleneck) step of the RAS chain [1], so renin inhibitors stop the cascade cold. “The advantage of blocking the biological pathway at the very beginning is that there is no downstream molecule interfering with anything,” said Dr. Jessica Mann, medical director at Speedel (http://www.speedel.com) a Swiss biotech company. Speedel, in conjunction with Novartis, will be the first to produce a new oral renin-inhibiting anti-hypertensive drug.

The Pit Viper Effect
The dangers associated with hypertension were recognized in the 1930s, but the first effective oral antihypertensive agents, diuretics, only appeared in the 1950s. Diuretics reduce blood pressure, in part, by increasing renal sodium excretion, thereby reducing the overall fluid volume in the body. They are still used today, both as first-line therapies and in combination with other drugs. Beta blockers were introduced in the 1970s, and calcium channel blockers in the 1980s. Beta blockers lower blood pressure by reducing the heart’s overall blood pumping capacity; they also decrease renin release from the kidney. Angiotensin-converting enzyme (ACE) inhibitors were developed in the mid 70s, as an indirect result of earlier experiments on the blood pressure-lowering effects of Brazilian pit viper venom. The first orally active ACE inhibitor, captopril, was approved by the FDA in 1981. Calcium channel blockers and ACE inhibitors both reduce blood pressure through their vasodilatory effects.

Angiotensin receptor type II blockers (ARBs) were first marketed in the U.S. in the mid 90s. ARBs inhibit the vasopressor effects of angiotensin II, the principal mediator of RAS downstream of renin production, by selectively blocking the AT1 receptors on the surface of target cells. By interfering with feedback inhibition, they increase angiotensin II levels. All or most of the deleterious effects of angiotensin II stimulation are mediated through the AT1 receptor. In most patients, a single antihypertensive agent does not succeed in reducing blood pressure to target levels, so various drug combinations are used, often including a low-dose diuretic. The side effects of antihypertensive agents vary: ARBs have the fewest side effects and, in most studies, exhibit a placebo-like tolerability profile.

Call Back When the Molecule Shapes Up
Speedel, now numbering over 70 employees, was founded in 1998 as an indirect result of the merger between Ciba-Geigy and Sandoz that formed Novartis. Dr. Alice Huxley was in charge of the early development of aliskiren at Ciba-Geigy, but the Novartis management decided to discard the compound, primarily because of its high cost of manufacturing. Novartis had other hypertension candidates at the time, including Diovan (valsartan). In 1999, Huxley and her colleagues licensed aliskiren under a “call back option,” meaning that if it successfully passed Phase II trials, Novartis would license it back for Phase III tests and commercialization.

“The synthesis of aliskiren was a major issue,” said Dr. Peter Herold, director of chemistry at Speedel, whose team did extensive molecular modeling and crystallographic structure analysis to optimize the drug. “Aliskiren has four chiral centers in the molecule. Mathematically, you have 16 possibilities. From Speedel Staunches the Renin Cascade at Its Source

People don’t die of high blood pressure on its own. People die of the long-term effects of high blood pressure on their hearts, their kidneys, and their brains.” According to Mann, despite great interest in renin inhibitors, pharmaceutical companies virtually abandoned them in the 1990s because they were large, complicated molecules, expensive to produce, and their bioavailability and potency were too low to be effective.

Speedel, in conjunction with Novartis, will be the first to produce a new oral renin-inhibiting anti-hypertensive drug.
a structural point of view, at the end of
the day, only one is the one you
want, as the others don’t fit in the en-
zyme.”

Aliskiren was licensed back by
Novartis in 2002 and is commercial-
ized under the trade name Tekturna.
Novartis recently announced favor-
able phase III data covering over
7000 patients with mild-to-moder-
ate hypertension in the U.S., E.U.
and Japan who were treated for
a period between 6 and 52 weeks.
Aliskiren was also tested in conjunc-
tion with a diuretic (HCTZ), a calcium
channel blocker (amlodipine), and
an ACE inhibitor (ramipril). The FDA
accepted aliskiren for regulatory
review in April 2006.

“The data, at least what I’ve seen
of it, looks pretty clean,” said Dr.
Alan Gradman, chief, division of
cardiovascular diseases, the West-
ern Pennsylvania Hospital, who was
involved with some of the aliskiren
clinical studies. According to Grad-
man, aliskiren lowers blood pres-
sure and has a comparable side
effect profile to anARB. “It is not
just about the hypertension and
hemodynamics, it is also about inhib-
itand organ damage effects that
occur with arteriosclerosis and left
ventricular hypertrophy and so on,”
said Gradman. “At this point in
time there is very little data on the
effects of aliskiren on any of these
endorgan effects. And part of the
problem is that you cannot really
study this well in animal models as
the compound is very specific for
human renin. What is interesting
about renin inhibitors is that they
antagonize the renin angiotensin
system through a different phar-
cologic mechanism than ACEs
and ARBs, so the question is what
effect they will have on the end
points?”

Speedel says that aliskiren, unlike
ACE inhibitors and ARBs, inhibits
renin, i.e., plasma renin activity
(PRA), a surrogate marker for heart
attacks and kidney disease. Grad-
man pointed out that Novartis is
now testing intermediate end points
such as proteinuria (protein in the
urine) to see if aliskiren attenuates
the progression of kidney disease
in patients. Novartis is also looking
at LVH regression (left ventricular
hypertrophy, the thickening of the
heart muscle that occurs as a result
of the heart having to contract
against higher pressures) for cardio-
vascular disease, but it will be diffi-
cult to see results without specific
trials measuring actual disease pro-
gression as an endpoint. Novartis is
also hypothesizing that combining
aliskiren with an ARB might provide
long-term organ protection because
there is no activation of RAS.

Speedel’s inaugural strategy was
to license promising cardiovascular
or metabolic drug candidates from
other companies, improve them, and
then license them back to pharma.
However, around 2002, Speedel
started their own internal develop-
ment program, Speedel Experi-
ments, now comprising 40 people.
Speedel financed itself by raising
U.S. $64 million through a sale of
500,000 treasury shares in March
2006. The company previously
raised U.S. $183 million from private
placements and two rounds of eq-
uity financing. Milestone revenues
have totaled U.S. $44 million so far.
Speedel is traded on the Swiss
stock exchange.

Aside from aliskiren, Speedel has
three other classes of renin inhibi-
tors: the 600 series in-licensed from
Roche; the 800 series, stemming
from a collaboration with Locus
Pharmaceuticals, now in preclinical
testing; and the 1100 series, devel-
oped internally. Speedel is also de-
veloping SPP301, an endothelin A
receptor antagonist for diabetic
neuropathy that is in Phase III trials,
and SPP200, an anticlotting agent
licensed from Abbott for vascular
graft occlusion, now in Phase II trials.

Renin Inhibitors Take Off
Speedel faces competition from
rival Swiss company, Actelion
(http://www.actelion.com) working
with Merck on a renin inhibitor that
entered human clinical trials in July
2006. “Aliskiren is still a substrate
peptidomimetic, whereas Actelion’s
compounds are nonsubstrate ana-
logs based on templates found origi-
nally by random screening,” said
Walter Fischli, Ph.D., head, drug dis-
covery, biochemistry, and molecular
biology at Actelion. “Before Acte-
lion’s breakthrough, pharmaceutical
companies large and small failed
to turn peptidomimetics into highly
bioavailable renin inhibitors. The
implications of low bioavailable
compounds are usually high doses
and variable pharmacologic results,
with the ultimate question [being]
whether a full blockade of the sys-
tem can be achieved at all.”

Vitae Pharmaceuticals, (http://
www.vitaepharma.com), a private
company based in Fort Washington,
PA, also has a renin inhibitor in preclinical development for hyper-
tension in conjunction with Glaxo-
SmithKline. The published literature
on renin inhibitors contains contri-
butions from other interested phar-
caceutical companies, including
Pfizer.

“Most of the renin inhibitors de-
veloped over the past two decades
were large molecules and couldn’t
get through the GI tract,” said Dr.
Randall Zusman, director of hyper-
tension and vascular medicine at
Massachusetts General Hospital.
“Aliskiren is a complex molecule,
but it has sufficient bioavailability
to inhibit renin activity in vivo, in
doses that do not induce adverse
side effects. Clinicians will be com-
paring these new drugs principally
to ACE inhibitors and ARBs. Is this
new strategy more effective than
what we have available, with fewer
side effects? A point in renin inhibi-
tor-based drugs’ favor is that they
have a very long half life (aliskiren
lasts approximately 40 hr). But until
they are used by a larger number of
patients, we don’t really know a
whole lot. The promise of this drug
is to disrupt the [renin] cascade
very early and be very complete in
its inhibitory effect.”

A century after Tiegerstadt
ground up rabbit kidneys and identi-
fied RAS, treating hypertension,
though considerably progressed, is
far from perfected. Time will tell
whether renin inhibitors fulfill their
promise, but as people age and
waistlines spread, increasing car-
diovascular and metabolic diseases
are sure to maintain the flow of
demand for new drugs.

Selected Reading
Renin inhibition: What are the therapeutic
opportunities? J. Am. Soc. Nephrol. 16,
592–599.

Wendy Wolfson (wendywolfson@nasw.org)
is a science technology writer based in
Oakland, CA.