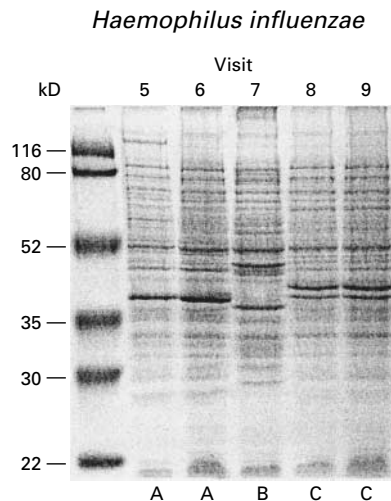




# This Week in the Journal

August 15, 2002

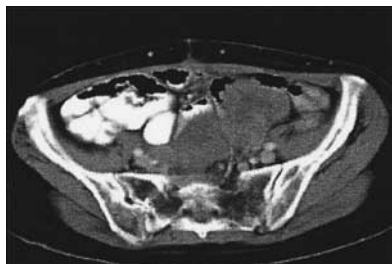


## New Strains of Bacteria and Exacerbations of Chronic Lung Disease

This prospective study examined the changes in bacterial isolates from sputum samples obtained monthly from 81 outpatients with chronic obstructive pulmonary disease. There were 374 acute exacerbations of lung disease, which were significantly associated with the acquisition of a new strain of *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae* (relative risk for any new strain, 2.15). An exacerbation was diagnosed at 33 percent of the clinic visits that coincided with the appearance of a new bacterial strain in the sputum.

*Earlier studies of chronic lung disease showed no association between clinical exacerbations and the presence of bacterial pathogens in the sputum. With the use of modern techniques to identify specific bacterial strains, this carefully performed study does show a relation between clinical deterioration and the presence of a new bacterial strain.*

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## Imatinib Mesylate in Advanced Gastrointestinal Stromal Tumors

Unresectable or metastatic gastrointestinal stromal tumors fail to respond to conventional chemotherapy and are usually fatal within 12 to 18 months. Most gastrointestinal stromal tumors have a defect in KIT, a transmembrane tyrosine kinase receptor. The abnormality prevents the death of the cell and forces it to proliferate. The effects of imatinib mesylate, which blocks the abnormal signaling by KIT, was studied in 147 patients with advanced gastrointestinal stromal tumors. There were no complete responses, but about half the patients had a stable partial response.

*This study of imatinib in a relatively large number of patients with a rare type of tumor yielded promising results. Longer follow-up will be needed to determine whether the drug really prolongs life. Nevertheless, these results in a disease with a generally hopeless prognosis are encouraging.*

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## PERSPECTIVE

## A Molecular Star in the Wars against Cancer

Eons ago, a retrovirus hijacked a gene from a chicken cell and enclosed it within its own genome. The captured gene was not idle, however: it gave the renegade virus the ability to cause tumors in chickens with amazing rapidity. The virus is the Rous sarcoma virus, the gene in the virus is called *v-src*, and the cellular gene is *c-src*. These discoveries shifted the tectonic plates of cancer research, thereby opening a new continent for exploration. The subsequent finding that *v-src* is a tyrosine kinase run wild substantiated the theory that cancer can originate from an unregulated cellular gene. To denote its potential to become a cancer-causing oncogene, *c-src* was named a proto-oncogene.

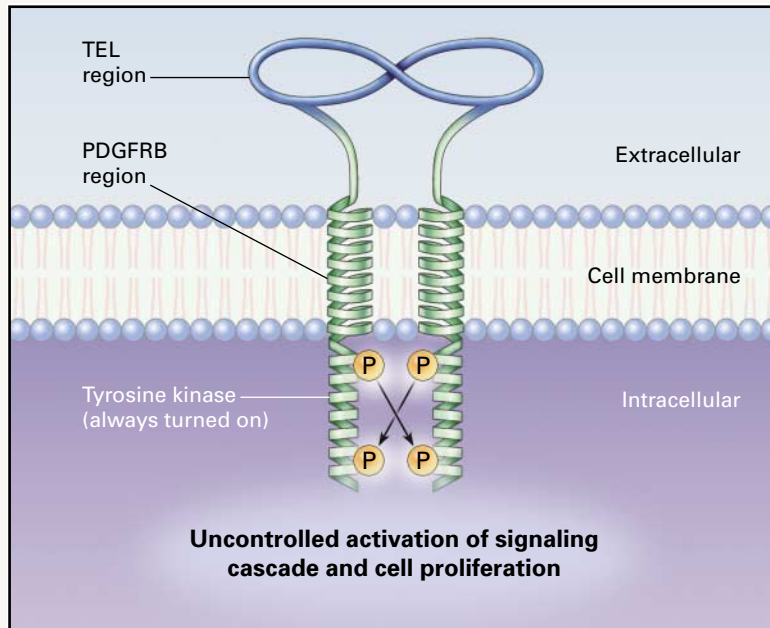
Tyrosine kinases like *src* catalyze protein phosphorylation and thereby regulate the protein's activity. They all have a binding site for ATP, the donor of phosphate groups to tyrosines in the target protein. The numerous tyrosine kinases have key roles in hundreds of the cell's activities; they are molecular devices that turn the activity of a protein on or off.

Some tyrosine kinases, termed receptor tyrosine kinases or transmembrane tyrosine kinases, have an intracellular kinase domain and an extracellular receptor domain. The insulin receptor is an example, but most other transmembrane tyrosine kinases are receptors for growth factors. Platelet-derived growth factor receptor beta (PDGFRB), for instance, stimulates cellular proliferation when it binds to its ligand, platelet-derived growth factor

(PDGF). The ligand bridges the gap between neighboring receptors (a process called dimerization), which allows adjoining tyrosine kinase domains to phosphorylate each other. The activated cytoplasmic chains then phosphorylate intracellular proteins that propagate the signal transmitted into the cell by the growth factor. KIT, another receptor tyrosine kinase, binds to a growth factor termed stem-cell factor and induces many kinds of cells to differentiate and proliferate. Not all tyrosine kinases are receptors. A kinase called ABL shuttles between the cytoplasm and the nucleus and participates in regulating the proliferation, adherence, and death (apoptosis) of cells. As would be expected, an enzyme with such pro-

tean activities is under tight regulation.

These three kinases, ABL, KIT, and PDGFRB, incite the development of chronic myelogenous leukemia (ABL), gastrointestinal stromal tumors (KIT), and a group of chronic myeloproliferative diseases characterized by eosinophilia (PDGFRB). In chronic myelogenous leukemia, a chromosomal rearrangement in a hematopoietic stem cell causes the formation of a fusion protein, BCR-ABL, in which the tyrosine kinase of the ABL portion is constitutively activated, rather than being tightly regulated. Moreover, unlike normal ABL, BCR-ABL is trapped in the cytoplasm, where its uncontrolled kinase activity stimulates proliferation



The TEL-PDGFRB Fusion Protein.

The extracellular growth factor-binding portion of PDGFRB has been amalgamated into an oncogenic protein by union with amino acid sequences derived from the TEL transcription factor. These sequences permanently dimerize the extracellular domain of PDGFRB, thereby causing constitutive autophosphorylation and activation of the intracellular tyrosine kinase region of the molecule. The activated kinase, in turn, activates a signaling cascade that induces cellular proliferation and blocks apoptosis.



## Imatinib Mesylate in Chronic Myeloproliferative Diseases

Imatinib mesylate blocks the activity of three protein tyrosine kinases: ABL, KIT, and platelet-derived growth factor receptor  $\beta$  (PDGFRB). These kinases have crucial roles in chronic myelogenous leukemia (ABL), gastrointestinal stromal tumors (KIT), and certain myeloproliferative diseases (PDGFRB). The first two types of neoplasms have been shown to respond to imatinib mesylate. This article reports that in four patients, a myeloproliferative disorder involving a rearranged *PDGFRB* gene also responded to the drug.

*These findings fulfill the prediction that a neoplasm that arises from an abnormality of the tyrosine kinase PDGFRB should respond to imatinib. Imatinib is an excellent example of an advance in medicine based on the fusion of molecular biology and molecular pharmacology.*

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and inhibits apoptosis. The term “gastrointestinal stromal tumor” refers to a group of neoplasms of spindle, smooth-muscle, or neural cells. They arise from a mutation of *c-KIT* that forces KIT to convey proliferative signals to the cell in the absence of its ligand. In the case of certain chronic myeloproliferative disorders, a chromosomal translocation joins the *PDGFRB* gene to a portion of the TEL protein (encoded by the *TEL* gene). The TEL portion dimerizes PDGFRB regions of the fusion protein, thereby constitutively activating their tyrosine kinase domains (see Figure). The result is an incessant stimulus to proliferate, as if PDGF were always bound to the receptor.

Imatinib mesylate (formerly STI571, now Gleevec in the United States and Glivec in Europe [Novartis]), a small organic compound, blocks the ATP-binding site of tyrosine kinases. It made its debut in chronic myelogenous leukemia, with the hope that it would block

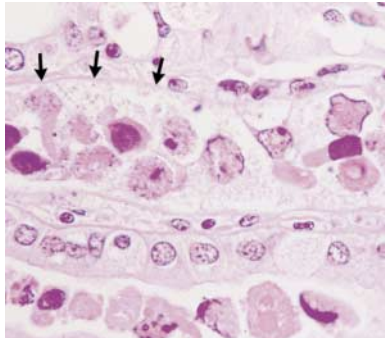
the tyrosine kinase activity of BCR-ABL. The results outstripped initial expectations. In this issue of the *Journal*, Demetri et al. (see pages 472–480) report that they tried imatinib therapy in 147 patients with unresectable, end-stage gastrointestinal stromal tumor, on the premise that it would inhibit the tyrosine kinase activity of the mutant KIT protein in that disease. About half the patients had partial remission while receiving the drug. Also in this issue, Apperley et al. (see pages 481–487) report the dramatic effect of imatinib in four patients with a myeloproliferative disease and a translocation involving *PDGFRB*.

Whether imatinib or similar compounds could be useful in other diseases is surely on the minds of many. At least seven families of transmembrane tyrosine kinases are receptors for growth factors with oncogenic potential. Some of these transmembrane tyrosine kinases may be targets for imatinib and related molecules. There are also

possibilities for using imatinib in combination with other drugs. One approach springs from the finding that when BCR-ABL is inactivated by imatinib, it can enter the nucleus, like normal ABL. An inhibitor of nuclear transport can trap BCR-ABL in the nucleus, and when imatinib is withdrawn, the nuclear BCR-ABL awakens and kills the cell.

These kinds of molecular war games could defeat the blast crisis of chronic myelogenous leukemia, which has not responded well to imatinib, and could be effective against imatinib-resistant chronic myelogenous leukemia. Imatinib is the first of a series of small, relatively nontoxic compounds that we will be hearing about. Now that the principles have been established, the field is wide open.

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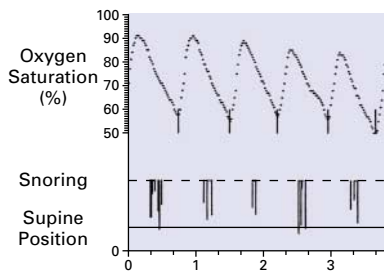


### Polyomavirus BK Replication and Allograft Nephropathy

Polyomavirus BK (BKV) nephropathy, an emerging cause of renal-allograft failure, may be linked to immunosuppressive regimens containing tacrolimus or mycophenolate mofetil. This prospective, single-center study examined urine for cells with viral inclusions, measured BKV DNA in plasma, and evaluated renal-biopsy specimens for evidence of nephropathy in 78 renal-transplant recipients who were being treated with such regimens. Four of five patients in whom BKV nephropathy developed were among the 77 percent of patients who had BKV antibodies before transplantation. The probability of BKV nephropathy was 8 percent (95 percent confidence interval, 1 to 15 percent).

*Cytologic analysis of urine and quantitative plasma polymerase-chain-reaction assays may be useful noninvasive methods of monitoring renal-transplant recipients for BKV replication and associated nephropathy.*

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### Clinical Practice: Obstructive Sleep Apnea

A 43-year-old man presents with heavy snoring; his bed partner reports that he sometimes stops breathing while he sleeps. He has hypertension controlled by medication but is otherwise healthy. He admits to feeling sleepy at times when he drives, although he has not had any motor vehicle accidents. His body-mass index is 33, and he has a large neck circumference (46 cm). How should he be evaluated and treated?

*This article discusses the diagnosis and management of obstructive sleep apnea.*

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Cutaneous lesion of leishmaniasis

### Current Concepts: Illness after International Travel

After international travel, up to 5 percent of travelers become ill enough to seek medical attention. This review focuses on the most common and most serious illnesses seen in persons from the industrialized world who have traveled to developing countries. The authors provide practical guidance for the diagnosis and management of fever, persistent diarrhea, and skin lesions in patients who present with these conditions after international travel.

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