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Janus kinase 2 (JAK2) is a cytoplasmic tyrosine kinase that transduces signals, especially those triggered by hematopoietic growth factors such as erythropoietin, in normal and neoplastic cells. In March and April 2005, four groups of investigators reported finding an acquired JAK2 mutation (termed JAK2 V617F) in association with polycythemia vera and related myeloproliferative disorders. These seminal reports have already been cited many times, and JAK2 is now a target for the development of new treatments for the myeloproliferative disorders. JAK2 V617F is detectable in more than 95% of patients who have polycythemia vera, as defined according to conventional criteria.


Two modern-day epidemics, HIV–AIDS and type 2 diabetes mellitus, have inspired impassioned calls for more effective interventions. In the 1980s, the rapid spread of HIV, with its associated severe, acute illness and high mortality, prompted activist groups and others to call for the accelerated approval of medications that showed promise of efficacy. There was no treatment available, and people were dying quickly. More recently, pressure to develop new drugs for type 2 diabetes has been stimulated by the remarkable worldwide increase in the incidence of this disease (54% in the past 7 years in the United States) and...


Pulmonary alveolar proteinosis is a rare disorder caused by abundant accumulation of surfactant-derived components in the lungs. The incidence is estimated to be 0.36 case per million population, and the prevalence, 3.70 cases per million.1 About 500 cases have been recorded in the literature. The condition usually presents as progressive dyspnea and a minimally productive cough. There are elevated serum levels of lactate dehydrogenase, which are associated with abnormal expiratory flow-volume curves, a restrictive ventilatory defect, and a disproportionate reduction in diffusing capacity. Patients often have hypoxemia, and...


On June 22, 2006, the nation of Ghana erupted. SUVs flew through the streets of Accra with flag-waving celebrants jammed through sunroofs. Crowds led by shirtless drummers banging garbage-can tops snaked down major roads, picking up revelers as they went. Hundreds of thousands of people took to the streets, shouting jubilantly. Ghana, playing in its first World Cup, had beaten the United States and earned a berth in the final stage of the global soccer pageant. It was a paroxysm of national pride that Ghana had rarely experienced. “It’s the same for football players as it is for doctors,” I was told by Tsiri paroxysm of national pride that Ghana had rarely experienced. “It’s the same for football players as it is for doctors,” I was told by Tsiri...
or nonfatal cardiovascular events, as confirmed by a review of medical records, including death from coronary heart disease or cerebrovascular disease, coronary revascularization, myocardial infarction, and stroke. In 2000, levels of PM2.5 exposure varied from 3.4 to 28.3 µg per cubic meter (mean, 13.5). Each increase of 10 µg per cubic meter was associated with a 24% increase in the risk of a cardiovascular event (hazard ratio, 1.24; 95% confidence interval [CI], 1.09 to 1.41) and a 76% increase in the risk of death from cerebrovascular disease (hazard ratio, 1.76; 95% CI, 1.25 to 2.47). For cardiovascular events, the between-city effect appeared to be smaller than the within-city effect. The risk of cerebrovascular events was also associated with increased levels of PM2.5 (hazard ratio, 1.35; 95% CI, 1.08 to 1.68). Long-term exposure to fine particulate air pollution is associated with the incidence of cardiovascular disease and death among postmenopausal women. Exposure differences within cities are associated with the risk of cardiovascular disease.

Krueger, GG, Richard G. Langley, Craig Leonard, Newman Yelding, Cynthia Guzzo, Yuhua Wang, Lisa T. Dooley, Mark Lebwohl. (2007). A Human Interleukin-12/23 Monoclonal Antibody for the Treatment of Psoriasis. New England Journal of Medicine, 356 (6), 580-592. Skin-infiltrating lymphocytes expressing type 1 cytokines have been linked to the pathophysiology of psoriasis. We evaluated the safety and efficacy of a human interleukin-12/23 monoclonal antibody in treating psoriasis. In this double-blind, placebo-controlled trial, 320 patients with moderate-to-severe plaque psoriasis underwent randomization to treatment with the interleukin-12/23 monoclonal antibody (one 45-mg dose, one 90-mg dose, four weekly 45-mg doses, or four weekly 90-mg doses) or placebo; 64 patients were randomly assigned to each group. Patients assigned to the interleukin-12/23 monoclonal antibody received one additional dose at week 16 if needed. Patients assigned to placebo crossed over to receive one 90-mg dose of interleukin-12/23 monoclonal antibody at week 20. There was at least 75% improvement in the psoriasis area-and-severity index at week 12 (the primary end point) in 52% of patients who received 45 mg of the interleukin-12/23 monoclonal antibody, in 59% of those who received 90 mg, in 67% of those who received four weekly 45-mg doses, and in 81% of those who received four weekly 90-mg doses, as compared with 2% of those who received placebo (P<0.001 for each comparison), and there was at least 90% improvement in 23%, 30%, 44%, and 52%, respectively, of patients who received the monoclonal antibody as compared with 2% of patients who received placebo (P<0.001 for each comparison). Adverse events occurred in 79% of patients treated with the interleukin-12/23 monoclonal antibody as compared with 72% of patients in the placebo group (P=0.19). Serious adverse events occurred in 4% of patients who received the monoclonal antibody and in 1% of those who received placebo (P=0.69). This study demonstrates the therapeutic efficacy of an interleukin-12/23 monoclonal antibody in psoriasis and provides further evidence of a role of the interleukin-12/23 p40 cytokines in the pathophysiology of psoriasis. Larger studies are needed to determine whether serious adverse events might limit the clinical usefulness of this new therapeutic target.

Legro, R.S., Huiman X.B, William D.S, Bruce R.C, Michael P.D, Sandra A.C, Michael P. S, Christos C, Peter G. M., Nicholas A. C, Gabriella G. G, John E. N, Linda C. G, Phyliss C. L, and Evan R. M. (2007). Clomiphene, Metformin, or Both for Infertility in the Polycystic Ovary Syndrome. New England Journal of Medicine, 356 (6), 551-566. The polycystic ovary syndrome is a common cause of infertility. Clomiphene and insulin sensitizers are used alone and in combination to induce ovulation, but it is unknown whether one approach is superior. We randomly assigned 626 infertile women with the polycystic ovary syndrome to receive clomiphene citrate plus placebo, extended-release metformin plus placebo, or a combination of metformin and clomiphene for up to 6 months. Medication was discontinued when pregnancy was confirmed, and subjects were followed until delivery. The live-birth rate was 22.5% (47 of 209 subjects) in the clomiphene group, 7.2% (15 of 208) in the metformin group, and 26.8% (56 of 209) in the combination-therapy group (P=0.001 for metformin vs. placebo, and combination therapy; P=0.31 for clomiphene vs. combination therapy). Among pregnancies, the rate of multiple pregnancy was 6.0% in the clomiphene group, 0% in the metformin group, and 3.1% in the combination-therapy group. The rates of first-trimester pregnancy loss did not differ significantly among the groups. However, the conception rate among subjects who ovulated was significantly lower in the metformin group (21.7%) than in either the clomiphene group (39.5%, P=0.002) or the combination-therapy group (46.0%, P<0.001). With the exception of pregnancy complications, adverse-event rates were similar in all groups, though gastrointestinal side effects were more frequent, and vasomotor and ophthalmic symptoms less frequent, in the metformin group than in the clomiphene group. Clomiphene is superior to metformin in achieving live birth in infertile women with the polycystic ovary syndrome, although multiple birth is a complication.

Linda M. Scott, Wei Tong, Ross L. Levine, Mike A. Scott, Philip A. Beer, Michael R. Stratton, P. Andrew Futreal, Wendy N. Erber, Mary Frances McMullin, Claire N. Harrison, Alan J. Warren, F.R.C.Path., F.Med.Sci., D. Gary Gilliland, Harvey F. Lodish, and Anthony R. Green. (2007). JAK2 Exon 12 Mutations in Polycythemia Vera and Idiopathic Erythrocytosis. New England Journal of Medicine, 356 (5), 459-468. The V617F mutation, which causes the substitution of phenylalanine for valine at position 617 of the Janus kinase (JAK) 2 gene (JAK2), is often present in patients with polycythemia vera, essential thrombocytopenia, and idiopathic myelofibrosis. However, the molecular basis of these myeloproliferative disorders in patients without the V617F mutation is unclear. We searched for new mutations in members of the JAK and signal transducer and activator of transcription (STAT) gene families in patients with V617F-negative polycythemia vera or idiopathic erythrocytosis. The mutations were characterized biochemically and in a murine model of bone marrow transplantation. We identified four somatic gain-of-function mutations affecting JAK2 exon 12 in 10 V617F-negative patients. Those with a JAK2 exon 12 mutation presented with an isolated erythrocytosis and distinctive bone marrow morphology, and several also had reduced serum erthropoietin levels. Erythroid colonies could be grown from their blood samples in the absence of exogenous erthropoietin. All such erythroid colonies were heterozygous for the mutation, whereas colonies homozygous for the mutation occur in most patients with V617F-positive polycythemia vera. BaF3 cells expressing the murine erthropoietin receptor and also carrying exon 12 mutations could proliferate without added interleukin-3. They also exhibited increased phosphorylation of JAK2 and extracellular regulated kinase 1 and 2, as compared with cells transduced by wild-type JAK2 or V617F JAK2. Three of the exon 12 mutations included a substitution of leucine for lysine at position 539 of JAK2. The V617F mutation, which causes the substitution of phenylalanine for valine at position 617 of the Janus kinase (JAK) 2 gene (JAK2), is often present in patients with polycythemia vera, essential thrombocytopenia, and idiopathic myelofibrosis. However, the molecular basis of these myeloproliferative disorders in patients without the V617F mutation is unclear. We searched for new mutations in members of the JAK and signal transducer and activator of transcription (STAT) gene families in patients with V617F-negative polycythemia vera or idiopathic erythrocytosis. The mutations were characterized biochemically and in a murine model of bone marrow transplantation. We identified four somatic gain-of-function mutations affecting JAK2 exon 12 in 10 V617F-negative patients. Those with a JAK2 exon 12 mutation presented with an isolated erythrocytosis and distinctive bone marrow morphology, and several also had reduced serum erthropoietin levels. Erythroid colonies could be grown from their blood samples in the absence of exogenous erthropoietin. All such erythroid colonies were heterozygous for the mutation, whereas colonies homozygous for the mutation occur in most patients with V617F-positive polycythemia vera. BaF3 cells expressing the murine erthropoietin receptor and also carrying exon 12 mutations could proliferate without added interleukin-3. They also exhibited increased phosphorylation of JAK2 and extracellular regulated kinase 1 and 2, as compared with cells transduced by wild-type JAK2 or V617F JAK2. Three of the exon 12 mutations included a substitution of leucine for lysine at position 539 of JAK2. This mutation resulted in a myeloproliferative phenotype, including JAK2 exon 12 mutations define a distinctive myeloproliferative syndrome that affects patients who currently receive a diagnosis of polycythemia vera or idiopathic erythrocytosis.


Increased mortality from infection in patients with pulmonary alveolar proteinosis occurs in association with high levels of autoantibodies against granulocyte–macrophage colony-stimulating factor (GM-CSF). We tested the hypothesis that neutrophil functions are impaired in patients with pulmonary alveolar proteinosis and that GM-CSF autoantibodies cause the dysfunction. We studied 12 subjects with pulmonary alveolar proteinosis, 61 healthy control subjects, and 12 control subjects with either cystic fibrosis or end-stage liver disease. We also studied GM-CSF–/– mice and wild-type mice. We evaluated basal neutrophil functions, neutrophil priming by CFM-CSF to augment antimicrobial functions, and the effects of highly purified GM-CSF autoantibodies on neutrophil functions in vitro and in vivo. Neutrophils from subjects with pulmonary alveolar proteinosis had normal ultrastructure and differentiation markers but impaired basal functions and antimicrobial functions after GM-CSF priming. GM-CSF–/– mice also had reduced basal neutrophil functions, but functions after GM-CSF priming were unimpaired. The neutrophil dysfunction characteristic of pulmonary alveolar proteinosis was reproduced in a dose-dependent fashion in blood specimens from healthy control subjects after incubation with affinity-purified GM-CSF autoantibodies isolated from patients with pulmonary alveolar proteinosis. The injection of mouse GM-CSF antibodies into wild-type mice also caused neutrophil dysfunction. The antimicrobial functions of neutrophils are impaired in patients with pulmonary alveolar proteinosis, owing to the presence of GM-CSF autoantibodies. The effects of these autoantibodies show that GM-CSF is an essential regulator of neutrophil functions.

SPECIAL ARTICLE


There is a need for close communication with relatives of patients dying in the intensive care unit (ICU). We evaluated a format that included a proactive end-of-life conference and a brochure to see whether it could lessen the effects of bereavement. Family members of 126 patients dying in 22 ICUs in France were randomly assigned to the intervention format or to the customary end-of-life conference. Participants were interviewed by telephone 90 days after the death of the patient. Providing relatives of patients who are dying in the ICU with a brochure on bereavement and using a proactive communication strategy that includes longer conferences and more time for family members to talk may lessen the burden of bereavement.


There is a heated debate about whether health professionals may refuse to provide treatments to which they object on moral grounds. It is important to understand how physicians think about their ethical rights and obligations when such conflicts emerge in clinical practice. We conducted a cross-sectional survey of a stratified, random sample of 2000 practicing U.S. physicians from all specialties by mail. The primary criterion variables were physicians’ judgments about their ethical rights and obligations when patients request a legal medical procedure to which the physician objects for religious or moral reasons. These procedures included administering terminal sedation in dying patients, providing abortion for failed contraception, and prescribing birth control to adolescents without parental approval. A total of 1144 of 1820 physicians (63%) responded to our survey. On the basis of our results, we estimate that most physicians believe that it is ethically permissible for doctors to explain their moral objections to patients (63%). Most also believe that physicians are obligated to present all options (86%) and to refer the patient to another clinician who does not object to the requested procedure (71%). Physicians who were male, those who were religious, and those who had personal objections to morally controversial clinical practices were less likely to report that doctors must disclose information about or refer patients for medical procedures to which the physician objected on moral grounds (multivariate odds ratios, 0.3 to 0.5). Many physicians do not consider themselves obligated to disclose information about or refer patients for legal but morally controversial medical procedures. Patients who want information about and access to such procedures may need to inquire proactively to determine whether their physicians would accommodate such requests.


Most cases of male prepubertal gynecomastia are classified as idiopathic. We investigated possible causes of gynecomastia in three prepubertal boys who were otherwise healthy and had normal serum concentrations of endogenous steroids. In all three boys, gynecomastia coincided with the topical application of products that contained lavender and tea tree oils. Gynecomastia resolved in each patient shortly after the use of products containing these oils was discontinued. Furthermore, studies in human cell lines indicated that the two oils had estrogenic and antiandrogenic activities. We conclude that repeated topical exposure to lavender and tea tree oils probably caused prepubertal gynecomastia in these boys.


Public reporting and pay for performance are intended to accelerate
improvements in hospital care, yet little is known about the benefits of these methods of providing incentives for improving care. We measured changes in adherence to 10 individual and 4 composite measures of quality over a period of 2 years at 613 hospitals that voluntarily reported information about the quality of care through a national public-reporting initiative, including 207 facilities that simultaneously participated in a pay-for-performance demonstration project funded by the Centers for Medicare and Medicaid Services; we then compared the pay-for-performance hospitals with the 406 hospitals with public reporting only (control hospitals). We used multivariable modeling to estimate the improvement attributable to financial incentives after adjusting for baseline performance and other hospital characteristics. As compared with the control group, pay-for-performance hospitals showed greater improvement in all composite measures of quality, including measures of care for heart failure, acute myocardial infarction, and pneumonia and a composite of 10 measures. Baseline performance was inversely associated with improvement; in pay-for-performance hospitals, the improvement in the composite of all 10 measures was 16.1% for hospitals in the lowest quintile of baseline performance and 1.9% for those in the highest quintile (P<0.001). After adjustments were made for differences in baseline performance and other hospital characteristics, pay for performance was associated with improvements ranging from 2.6 to 4.1% over the 2-year period.

CLINICAL THERAPEUTICS
(Since these articles have no abstract, we just provided an extract of the first 100 words of the full text and any section headings)


This Journal feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the authors’ clinical recommendations.

CLINICAL PRACTICE
(Since these articles have no abstract, we just provided an extract of the first 100 words of the full text and any section headings)


This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author’s clinical recommendations. A 68-year-old woman is incidentally found to have a left adrenal mass, 2.8 cm in diameter, on abdominal computed tomography that was ordered to evaluate right lower abdominal discomfort (which has since resolved). Her medical history is notable...

IMAGES IN CLINICAL MEDICINE
(Since these articles have no abstract, we just provided an extract of the first 100 words of the full text and any section headings)


A 45-year-old healthy man was involved in demolishing an industrial plant in which glass had been etched. He was exposed to a reservoir of 70% hydrofluoric acid while repairing a pipeline. He was admitted to the intensive care unit for second-degree and third-degree burns from hydrofluoric acid affecting 30% of his body-surface area, including both hands, both forearms, the chest, back, scalp, and neck. After penetrating tissue, hydrofluoric acid dissociates into hydrogen and fluoride ions, of which particularly fluoride is toxic. Since fluoride ions are inactivated by means of precipitation with calcium and magnesium, the infusion of calcium and magnesium is considered a therapy in patients with hydrofluoric acid burns. In this patient, magnesium was infused intravenously, and calcium was infused intravenously and intraarterially (through the brachial artery) and was applied topically to the burned skin. The blood magnesium level was always within the normal range during substitution therapy. Blood levels of ionized calcium were initially elevated to up to 1.75 mmol per liter but were within the normal range after 36 to 48 hours. As a result of this intense calcium and magnesium therapy, cutaneous calcification developed on the fingertips by 36 to 48 hours, as well as on the dorsal and palmar aspects of the hand (Panels A and B, respectively). Three months later, the patient had regained an almost full range of motion, was free of symptoms, and had a good aesthetic result.


A 38-year-old man presented to the emergency department after reportedly ingesting antifreeze. He appeared to be intoxicated and was agitated and combative; chemical sedation was induced. Initial laboratory studies revealed a pH of 7.0, an anion gap of 22 mmol per liter, and an osmolar gap of 79 mOsm. It was noted that the patient’s urine fluoresced under ultraviolet light (in the basin on the left), as compared with a negative control (in the basin on the right), which shows the purple reflection of the ultraviolet light (arrow). The patient received fomepizole, thiamine, folate, pyridoxine, and bicarbonate; he subsequently underwent...

CLINICAL PROBLEM-SOLVING
(Since these articles have no abstract, we just provided an extract of the first 100 words of the full text and any section headings)


A 50-year-old Asian woman presented with a papulonodular, erythematous rash on her legs below the knees. The skin lesions were nontender and nonpruritic and were accompanied by paresthesias. She had no fever, arthralgias, or other systemic symptoms. The papulonodular rash on the legs coupled with paresthesias raises the possibility of a diagnosis of erythema nodosum. Erythema nodosum can develop as a delayed . . .
**Engl. Journal of Medicine, 356(6), e5.**

A 56-year-old woman was admitted to the hospital because of rapidly progressive vertigo and ataxia. The patient had been well until approximately 10 weeks before admission, when occasional dizziness and nausea occurred, followed during the next several weeks by increasing positional vertigo and severe vomiting. Antiemetic agents were administered, the vomiting resolved, and her dizziness improved. Shortly thereafter, slurred speech, rapidly progressive ataxia, and difficulty with ambulation developed.

**Editorials**

(Since these articles has no abstract, we just provided an extract of the first 100 words of the full text and any section headings)


It is hard to dispute the rationale behind realigning payment incentives in health care to encourage higher quality and more efficient care. Indeed, across the country and beyond, the number of “pay for performance” programs, as such realignment is called, has reached a tipping point. In the United States, more than half the health maintenance organizations (HMOs) in the private sector have now initiated such programs, covering more than 80% of the country’s HMO enrollees.1 Congress has mandated that the Center for Medicare and Medicaid Services (CMS) develop plans to introduce a pay-for-performance program into Medicare.2 The British . . .


Critical care services are highly valued because they can often restore function in patients with acute life-threatening illnesses. In this context, advances in medical science have led to increased expectations for favorable outcomes of episodes of critical illness, even when the patient has severe coexisting chronic disease. The growing demand for critical care has led both to increased numbers of patients who survived with desirable functional outcomes and to increased numbers of patients who die in the intensive care unit (ICU). Today, many deaths in the ICU occur after a decision has been made to discontinue or forgo advanced supportive . . .


More than a decade ago, prospective epidemiologic studies showed that mortality was increased among people living in communities with elevated concentrations of fine particulate air pollution.1,2 Subsequent research has shown that particulate air pollution is statistically and mechanistically linked to increased cardiovascular disease.3 New data are beginning to shed light on which persons are at heightened risk. In this issue of the Journal, Miller et al.4 report on data from the Women’s Health Initiative (WHI) observational study, which greatly expands our understanding of how fine particulate pollution affects health. Earlier long-term prospective cohort studies showed an association between levels of air pollution consisting of particulate matter.


Of the estimated 6.7 million women with fertility problems in the United States, 35% have received drugs to induce ovulation.1 The most common cause of anovulation among infertile women is the polycystic ovary syndrome, a condition typically characterized by irregular menses, androgen excess, and polycystic-appearing ovaries. The condition is associated with insulin resistance and obesity. Although a number of drugs have been used to induce ovulation in women with the polycystic ovary syndrome, clomiphene citrate is a simple, tried-and-true treatment. Clomiphene is an orally active, antiestrogenic substance that promotes the release of follicle-stimulating hormone from the pituitary gland, thus . . .

**Clinical Implications of Basic Research**


When the causative gene for Huntington’s disease was identified in 1993, there was great anticipation and hope that key disease-causing mechanisms would be identified quickly and that rational neuroprotective treatments would soon follow. Fourteen years later, it is obvious we were wrong. Potential pathogenic mechanisms have proliferated, and their relative importance is unclear. Now, three recent studies1,2,3 have identified a protein and a mechanism that link two of the leading hypotheses of pathogenesis: transcriptional dysregulation and mitochondrial impairment (Figure 1). . .

**Health Policy Report**


The modern hospital bears little resemblance to its ancestors. The charitable institutions of the 19th century mainly tended, rather than treated, the sick, and they served mostly poor patients, whereas the wealthy received care at home. The transformation of hospitals “from places of dreaded impurity and exiled human wreckage into awesome citadels of science and bureaucratic order”1 occurred during the 20th century, thanks to scientific advances and the maturation of the medical profession and the health insurance industry.2 Hospitals today are big businesses that derive most of their revenues from paying patients and health care insurers. . .