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# Table of Contents

## Perspectives

**Going Dutch: managed-competition health insurance in the Netherlands.**
Enthoven, A.C., and Wynand P.M.M. van de Ven

**Dutch doctors and their patients: effects of health care reform in the Netherlands.**
J. André Knottnerus, and Gabriël H.M. ten Velden.

**Childhood obesity: the shape of things to come.**
Ludwig, D.S.

**Knock out, Knock in, Knock down: genetically manipulated mice and the Nobel Prize.**
Manis, J.P.

## Articles

**Childhood body-mass index and the risk of coronary heart disease in adulthood.**

**Cardiac-resynchronization therapy in heart failure with narrow QRS complexes.**

**Respiratory effects of exposure to diesel traffic in persons with asthma.**
Cullinan, I., Mark J. Nieuwenhuijsen, James Stewart-Evans, Eleni Malliarou, Lars Jarup, Robert Harrington, Magnus Svartengren, In-Kyu Han, Pamela Ohman-Strickland, Kian Fan Chung, and Junfeng Zhang.

**Reduced exposure to PM10 and attenuated age-related decline in lung function.**

**Outcomes 18 months after the first human partial face transplantation.**
Dubernard, J.-M., Benoît Lenglé, Emmanuel Morelon, Sylvie Testelin, Lionel Badet, Christophe Moure, Jean-Luc Beziat, Stéphanie Dakpé, Jean Kanitakis, Cédric D'Hauthuille, Assia El Jaafari, Palmina Petruzzo, Nicole Lefrançois, Farid Taha, Angela Sirigu, Giovanni Di Marco, Esther Carmi, Danielle Bachmann, Sophie Cremades, Pascal Giraux, Gabriel Burloux, Olivier Hequet, Nathalie Parquet, Camille Francès, Mauricette Michallet, Xavier Martin, and Bernard Devauchelle.

**Metabolic effects of a growth hormone–releasing factor in patients with HIV.**
Falutz, J., Soraya Allas, Koenraad Blot, Diane Potvin, Donald Kotler, Michael Somero, Daniel Berger, Stephen Brown, Gary Richmond, Jeffrey Fessel, Ralph Turner, and Steven Grinspoon.

**Corticosteroids for bacterial meningitis in adults in sub-Saharan Africa.**

**Dexamethasone in Vietnamese adolescents and adults with bacterial meningitis.**

## Special Article

**Adolescent overweight and future adult coronary heart disease.**
Bibbins-Domingo, K., Pamela Coxson, Mark J. Pletcher, James Lightwood, and Lee Goldman.

## Review Article

**Platelet activation and atherothrombosis.**
Giovanni Davi, and Carlo Patrono.
PERSPECTIVES


Twenty-five years ago, the health care system of the Netherlands was operating under top-down cost-containment policies, such as regulation of doctors’ fees and hospital budgets, that were widely criticized for lacking incentives for efficiency and innovation. In 1986, the Dekker Committee, an independent group appointed by the Dutch government to seek a solution, recommended market-oriented reform within the context of a national health insurance system. But before the concept could be implemented, a host of adequate systems had to be developed — systems of risk equalization, of product classification and medical pricing to give providers appropriate incentives for efficiency, of . . .


It is still too early to draw definitive conclusions about the effects of the reform of the Dutch health care system, which was implemented in 2006. But physicians and patients are now living under the new system, and some of its consequences are becoming clear. Primary care has been at the center of Dutch health care practice for a long time. All citizens are registered with a general practitioner, who provides generalist and continuous medical care and deals with more than 95% of health problems. Specialist consultations are covered by insurance only after referral. Since World War II, insurance coverage . . .


Last week, I met with the G. family in the Optimal Weight for Life (OWL) clinic at my hospital. One of the parents was overweight, and the other was obese. The five children were more severely obese and had numerous weight-related complications — one had evidence of fatty liver, one had high blood pressure, two had gastroesophageal reflux, two had orthopedic problems, three had marked insulin resistance, four had dyslipidemia, and all had emotional problems related to their weight. Sadly, this family might be a microcosm of 21st-century America: if we don’t take steps to reverse course, the children of . . .

CLINICAL THERAPEUTICS

IMAGES IN CLINICAL MEDICINE
Reversal of laryngeal paresis. Lewin, J.S., and Zinner, R.G.
Lingua villosa nigra. Ramsakal, A., and Mangat, L.
Dissecting aneurysm of the posterior cerebral artery. Renard, D., and Milhaud, D.
Occlusion and reperfusion of the middle cerebral artery. Ryan, R., and Brophy, D.P.

VIDEOS IN CLINICAL MEDICINE

CLINICAL PROBLEM-SOLVING

CLINICAL PRACTICE
Erectile dysfunction. McVary, K.T.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

In Stockholm this fall, the Nobel Prize in Medicine or Physiology was awarded to Martin Evans, Oliver Smithies, and Mario Capecchi for their discoveries of “principles for introducing specific gene modifications in mice by the use of embryonic stem cells.” The methods they developed make possible exquisitely detailed studies of the function of almost any gene in a living animal. Given the high degree of similarity between the mouse and human genomes, this technology of gene manipulation has important clinical implications. The concept of genetically engineering a mouse is straightforward: devise a specific genetic modification in a chromosome of embryonic . . .


In recent weeks, over-the-counter cough and cold medications for children have received unprecedented attention from regulators, physicians, the media, and parents. This scrutiny represents a long-overdue reassessment of products that were purchased by 39% of U.S. households during the past 3 years. It also reflects an important evolution in the standard of evidence for medications used in children. Over-the-counter cough and cold preparations include various combinations of antihistamines, decongestants, antitussives, and expectorants. There is no standard for describing these products; two products marketed similarly may have different types of ingredients (see table). Consumers purchase about 95 million packages of . . .

ARTICLES


The worldwide epidemic of childhood obesity is progressing at an alarming rate. Risk factors for coronary heart disease (CHD) are already identifiable in overweight children. The severity of the long-term effects of excess childhood weight on CHD, however, remains unknown. We investigated the association between body-mass index (BMI) in childhood (7 through 13 years of age) and CHD in adulthood (25 years of age or older), with and without adjustment for birth weight. The subjects were a cohort of 276,835 Danish schoolchildren for whom measurements of height and weight were available. CHD events were ascertained by linkage to national registers. Cox regression analyses were performed. In 5,063,622 person-years of follow-up, 10,235 men and 4318 women for whom childhood BMI data were available received a diagnosis of CHD or died of CHD as adults. The risk of any CHD event, a nonfatal event, and a fatal event among adults was positively associated with BMI at 7 to 13 years of age for boys and 10 to 13 years of age for girls. The associations were linear for each age, and the risk increased across the entire BMI distribution. Furthermore, the risk increased as the age of the child increased. Adjustment for birth weight strengthened the results. Higher BMI during childhood is associated with an increased risk of CHD in adulthood. The associations are stronger in boys than in girls and increase with the age of the child in both sexes. Our findings suggest that as children are becoming heavier worldwide, greater numbers of them are at risk of having CHD in adulthood.


Some patients with narrow QRS complexes have echocardiographic evidence of left ventricular mechanical dyssynchrony and may also benefit from CRT. We enrolled 172 patients who had a standard indication for an implantable cardioverter–defibrillator. Patients received the CRT device and were randomly assigned to the CRT group or to a control group (no CRT) for 6 months. The primary end point was the proportion of patients with an increase in peak oxygen consumption of at least 1.0 ml per kilogram of body weight per minute during cardiopulmonary exercise testing at 6 months. At 6 months, the CRT group and the control group did not differ significantly in the proportion of patients with the primary end point (46% and 41%, respectively). In a prespecified subgroup with a QRS interval of 120 msec or more, the peak oxygen consumption increased in the CRT group (P=0.02), but it was unchanged in a subgroup with a QRS interval of less than 120 msec (P=0.45). There were 24 heart-failure events requiring intravenous therapy in 14 patients in the CRT group (16.1%) and 41 events in 19 patients in the control group (22.3%), but the difference was not significant. CRT did not improve peak oxygen consumption in patients with moderate-to-severe heart failure, providing evidence that patients with heart failure and narrow QRS intervals may not benefit from CRT.
Air pollution from road traffic is a serious health hazard, and people with preexisting respiratory disease may be at increased risk. We investigated the effects of short-term exposure to diesel traffic in people with asthma in an urban, roadside environment. We recruited 60 adults with either mild or moderate asthma to participate in a randomized, crossover study. Each participant walked for 2 hours along a London street (Oxford Street) and, on a separate occasion, through a nearby park (Hyde Park). We performed detailed real-time exposure, physiological, and immunologic measurements. Participants had significantly higher exposures to fine particles (<2.5 μm in aerodynamic diameter), ultrafine particles, elemental carbon, and nitrogen dioxide on Oxford Street than in Hyde Park. Walking for 2 hours on Oxford Street induced asymptomatic but consistent reductions in the forced expiratory volume in 1 second (FEV1) (up to 6.1%) and forced vital capacity (FVC) (up to 5.4%) that were significantly larger than the reductions in FEV1 and FVC after exposure in Hyde Park (P=0.04 and P=0.01, respectively, for the overall effect of exposure, and P<0.005 at some time points).


Air pollution has been associated with impaired health, including reduced lung function in adults. Moving to cleaner areas has been shown to attenuate adverse effects of air pollution on lung function in children but not in adults. We conducted a prospective study of 9651 adults (18 to 60 years of age) randomly selected from population registries in 1990 and assessed in 1991, with 8047 participants reassessed in 2002. There was complete information on lung volumes and flows (e.g., forced vital capacity [FVC], forced expiratory volume in 1 second [FEV1], FEV1 as a percentage of FVC, and forced expiratory flow between 25 and 75% of the FVC [FEF25–75]), smoking habits, and spatially resolved concentrations of particulate matter that was less than 10 μm in aerodynamic diameter (PM10) from a validated dispersion model assigned to residential addresses for 4742 participants at both the 1991 and the 2002 assessments and in the intervening years. Overall exposure to individual home outdoor PM10 declined over the 11-year follow-up period (median, –5.3 μg per cubic meter; interquartile range, –7.5 to –4.2). In mixed-model regression analyses, with adjustment for confounders, PM10 concentrations at baseline, and clustering within areas, there were significant negative associations between the decrease in PM10 and the rate of decline in FEV1 (P<0.045), FEV1 as a percentage of FVC (P=0.02), and FEF25–75 (P=0.001). The net effect of a decline of 10 μg of PM10 per cubic meter over an 11-year period was to reduce the annual rate of decline in FEV1 by 9% and of FEF25–75 by 16%. Cumulative exposure in the interval between the two examinations showed similar associations. Decreasing exposure to airborne particulates appears to attenuate the decline in lung function related to exposure to PM10. The effects are greater in tests reflecting small-airway function.


We performed the first human partial face allograft on November 27, 2005. Here we report outcomes up to 18 months after transplantation. The postsurgical induction immunosuppression protocol included thymoglobulins combined with tacrolimus, mycophenolate mofetil, and prednisone. Donor hematopoietic stem cells were infused on postoperative days 4 and 11. Sequential biopsy specimens were taken from a sentinel skin graft, the facial skin, and the oral mucosa. Functional progress was assessed by tests of sensory and motor function performed monthly. Psychological support was provided before and after transplantation. Sensitivity to light touch, as assessed with the use of static monofilaments, and sensitivity to heat and cold had returned to normal
at 6 months after transplantation. Motor recovery was slower, and labial contact allowing complete mouth closure was achieved at 10 months. Psychological acceptance of the graft progressed as function improved. Rejection episodes occurred on days 18 and 214 after transplantation and were reversed. A decrease in inulin clearance led to a change in immunosuppressive regimen from tacrolimus to sirolimus at 14 months. Extracorporeal photochemotherapy was introduced at 10 months to prevent recurrence of rejection. There have been no subsequent rejection episodes. At 18 months, the patient is satisfied with the aesthetic result. In this patient who underwent the first partial face transplantation, the functional and aesthetic results 18 months after transplantation are satisfactory.


Visceral adipose tissue accumulates during antiretroviral therapy in many patients who are infected with the human immunodeficiency virus (HIV); this process is associated with an increased cardiovascular risk. We assessed the use of a growth hormone–releasing factor analogue, tesamorelin, to decrease visceral adiposity. We randomly assigned 412 patients with HIV (86% of whom were men) who had an accumulation of abdominal fat to receive a daily subcutaneous injection of either 2 mg of tesamorelin or placebo for 26 weeks. The primary end point was the percent change from baseline in visceral adipose tissue as shown on computed tomography. Secondary end points included triglyceride levels, the ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol, the level of insulin-like growth factor I (IGF-I), and self-assessed body image. Glycemic measures included glucose and insulin levels. The measure of visceral adipose tissue decreased by 15.2% in the tesamorelin group and increased by 5.0% in the placebo group; the levels of triglycerides decreased by 50 mg per deciliter and increased by 9 mg per deciliter, respectively, and the ratio of total cholesterol to HDL cholesterol decreased by 0.31 and increased by 0.21, respectively (P<0.001 for all comparisons). Levels of total cholesterol and HDL cholesterol also improved significantly in the tesamorelin group. Levels of IGF-I increased by 81.0% in the tesamorelin group and decreased by 5.0% in the placebo group (P<0.001). Adverse events did not differ significantly between the two study groups, but more patients in the tesamorelin group withdrew from the study because of an adverse event. No significant differences were observed in glycemic measures. Daily tesamorelin for 26 weeks decreased visceral fat and improved lipid profiles, effects that might be useful in HIV-infected patients who have treatment-associated central fat accumulation.


In sub-Saharan Africa, bacterial meningitis is common and is associated with a high mortality. Adjuvant therapy with corticosteroids reduces mortality among adults in the developed world, but it has not been adequately tested in developing countries or in the context of advanced human immunodeficiency virus (HIV) infection. We conducted a randomized, double-blind, placebo-controlled trial of dexamethasone (16 mg twice daily for 4 days) and an open-label trial of intramuscular versus intravenous ceftriaxone (2 g twice daily for 10 days) in adults with an admission diagnosis of bacterial meningitis in Blantyre, Malawi. The primary outcome was death at 40 days after randomization. A total of 465 patients, 90% of whom were HIV-positive, were randomly assigned to receive dexamethasone (233 patients) or placebo (232 patients) plus intramuscular ceftriaxone (230 patients) or intravenous ceftriaxone (235 patients). There was no significant difference in mortality at 40 days in the corticosteroid group (129 of 231 patients) as compared with the placebo group (120 of 228 patients) by intention-to-treat analysis (odds ratio, 1.14; 95% confidence interval [CI], 0.79 to 1.64) or when the analysis was restricted to patients with proven pneumococcal meningitis (68 of 129 patients receiving corticosteroids vs. 72 of 143 patients receiving placebo) (odds ratio, 1.10; 95% CI, 0.68 to 1.77). There were no significant differences between groups in the outcomes of disability and death combined, hearing impairment, and adverse events. There was no difference in mortality with intravenous ceftriaxone (121 of 230 patients) as compared with intramuscular ceftriaxone (128 of 229 patients) (odds ratio, 0.88; 95% CI, 0.61 to 1.27). Adjuvant therapy with dexamethasone for bacterial meningitis in adults from an area with a high prevalence of HIV did not reduce mortality or morbidity. In this setting, intramuscular administration was not inferior to intravenous administration of ceftriaxone for bacterial meningitis.
It is uncertain whether all adults with bacterial meningitis benefit from treatment with adjunctive dexamethasone. We conducted a randomized, double-blind, placebo-controlled trial of dexamethasone in 435 patients over the age of 14 years who had suspected bacterial meningitis. The goal was to determine whether dexamethasone reduced the risk of death at 1 month and the risk of death or disability at 6 months. A total of 217 patients were assigned to the dexamethasone group, and 218 to the placebo group. Bacterial meningitis was confirmed in 300 patients (69.0%), probable meningitis was diagnosed in 123 patients (28.3%), and an alternative diagnosis was made in 12 patients (2.8%). An intention-to-treat analysis of all the patients showed that dexamethasone was not associated with a significant reduction in the risk of death at 1 month (relative risk, 0.79; 95% confidence interval [CI], 0.45 to 1.39) or the risk of death or disability at 6 months (odds ratio, 0.74; 95% CI, 0.47 to 1.17). In patients with confirmed bacterial meningitis, however, there was a significant reduction in the risk of death at 1 month (relative risk, 0.43; 95% CI, 0.20 to 0.94) and in the risk of death or disability at 6 months (odds ratio, 0.56; 95% CI, 0.32 to 0.98). These effects were not found in patients with probable bacterial meningitis. Results of multivariate analysis indicated that dexamethasone treatment for patients with probable bacterial meningitis was significantly associated with an increased risk of death at 1 month, an observation that may be explained by cases of tuberculous meningitis in the treatment group. Dexamethasone does not improve the outcome in all adolescents and adults with suspected bacterial meningitis; a beneficial effect appears to be confined to patients with microbiologically proven disease, including those who have received prior treatment with antibiotics.

The effect of adolescent overweight on future adult coronary heart disease (CHD) is not known. We estimated the prevalence of obese 35-year-olds in 2020 on the basis of adolescent overweight in 2000 and historical trends regarding overweight adolescents who become obese adults. We then used the CHD Policy Model, a state-transition computer simulation of U.S. residents who are 35 years of age or older, to project the annual excess incidence and prevalence of CHD, the total number of excess CHD events, and excess deaths from both CHD and other causes attributable to obesity from 2020 to 2035. We also modeled the effect of treating obesity-related increases in blood pressure and dyslipidemia. Adolescent overweight is projected to increase the prevalence of obese 35-year-olds in 2020 to a range of 30 to 37% in men and 34 to 44% in women. As a consequence of this increased obesity, an increase in the incidence of CHD and in the total number of CHD events and deaths is projected to occur in young adulthood. The increase is projected to continue in both absolute and relative terms as the population reaches middle age. By 2035, it is estimated that the prevalence of CHD will increase by a range of 5 to 16%, with more than 100,000 excess cases of CHD attributable to the increased obesity.

Platelets are essential for primary hemostasis and repair of the endothelium, but they also play a key role in the development of acute coronary syndromes and contribute to cerebrovascular events. In addition, they participate in the process of forming and extending atherosclerotic plaques. Atherosclerosis is a chronic inflammatory process,1 and inflammation is an important component of acute coronary syndromes.2 The relation between chronic and acute vascular inflammation is unclear, but platelets are a source of inflammatory mediators,3 and the activation of platelets by inflammatory triggers may be a critical component of atherothrombosis.4 This review article describes the role of platelets . . .
CLINICAL THERAPEUTICS


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. A 4-month-old baby girl whose parents and 6-year-old brother have severe-to-profound sensorineural hearing loss is referred for consideration for cochlear implantation. Each of the baby's parents had previously received a cochlear implant in adulthood, and her older brother had . . .

IMAGES IN CLINICAL MEDICINE


A 51-year-old man with stage IV non–small-cell lung cancer, who was receiving chemotherapy, had hoarseness and weak vocal intensity, which developed over a period of 3 days, progressing to near-complete aphony. Computed tomography of the chest showed an enlarged left paratracheal lymph node (Panel A, arrow), and videostroboscopy (Panel B, vocal cords open; Panel C, vocal cords closed; Video 1 [arrows in Panels B, C, E, and F indicate posterior direction, arrowheads left cord]) showed severe left vocal cord paresis, with early atrophy and bowing. A granulomatous lesion on the posterior cord (Panel B, short arrow) was consistent with the . . .


A 24-year-old man presented with black discoloration and hairy appearance of his tongue, which he had had for 2 days, and a sore throat. He had been taking ciprofloxacin and doxycycline for the past week for an upper respiratory tract infection. He did not smoke or use oral tobacco products, and he was not taking any bismuth-containing compounds. Physical examination revealed white tonsillar exudates and a black discoloration of the tongue; no fever, adenopathy, or hepatosplenomegaly was noted. The results of a rapid streptococcal-antigen test and a monospot test were negative. A throat culture was positive for Candida albicans. . . .


A 43-year-old man presented with acute-onset hemianesthesia involving the right arm, the right leg, and the right side of the face. Six weeks earlier, he had a moderate occipital headache that lasted for 3 days. Diffusion-weighted magnetic resonance imaging (MRI) of the brain showed a thalamic lesion of restricted diffusion on the left side (Panel A, arrow), which was consistent with acute posterior choroidal-artery infarction. T2-weighted MRI scans, a magnetic resonance angiogram, and a computed tomographic angiogram (Panels B, C, and D, respectively) revealed a dilatation of the left posterior cerebral artery, with a double lumen — that is, . . .


A 65-year-old woman with chronic atrial fibrillation was admitted for an elective exchange of an implanted defibrillator for idiopathic dilated cardiomyopathy. To facilitate this procedure, warfarin was withheld for 5 days. Before the procedure was performed, acute-onset right hemiparesis and expressive dysphasia developed. Urgent noncontrast computed tomography (CT) of the brain and CT angiography of the intracranial and extracranial arterial circulation confirmed an acute occlusion of the M2 segment of the middle cerebral artery, which was consistent with the presence of an embolus (Panel A, arrow). Ninety-five minutes after the onset of neurologic deficits, the patient was given a bolus . . .

VIDEOS IN CLINICAL MEDICINE


Evidence suggests that the risk of major central venous line complications, particularly line-related bloodstream infections, is lower when the subclavian approach is used. This video will identify the landmarks and procedure for placement of a subclavian central line. Specific contraindications for the placement of a central venous line in the subclavian vein include infection of the area overlying the target vein and thrombosis of the target vein and fracture or suspected fracture of the clavicle or proximal ribs. Coagulopathy, while not an absolute contraindication, should be of greater concern
with the subclavian approach because of the difficulty in applying . . .

CLINICAL PROBLEM-SOLVING


In this Journal feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information, sharing his or her reasoning with the reader (regular type). The authors’ commentary follows. A 23-year-old black woman presented to the emergency department with diffuse, colicky abdominal pain of 1 hour’s duration. The pain was followed by nausea and episodes of bilious vomiting and did not radiate or change with the patient’s position. She did not report fever, chills, diarrhea, hematochezia, or melena. The differential diagnosis of acute abdominal pain in young adults is broad and . . .

CLINICAL PRACTICE


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 65-year-old man presents to an outpatient clinic, reporting that he can no longer maintain an erection sufficient for intercourse. His medical history includes well-controlled hypertension and stable coronary artery disease. He smokes a pack of cigarettes daily. His medications include atenolol and low-dose aspirin (81 mg daily). On physical examination, his body-mass index (the weight in kilograms divided by the square . . .

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL


Dr. Michael Sherling (Dermatology): A 44-year-old woman was admitted to this hospital because of generalized, painful, ulcerated cutaneous lesions. The patient had been well, except for eczema, until 4 years before admission, when erosions on the scalp developed, followed by a generalized papular skin eruption. Betamethasone dipropionate and cephalexin were prescribed, without improvement. Examination by a dermatologist 2.3 years before admission revealed scarring alopecia and multiple hyperkeratotic erythematous plaques on the trunk and arms. Pathological examination of biopsy specimens of two lesions on the left arm were reported to show hypertrophic lichenoid dermatitis with eosinophilia. The results of laboratory tests . . .