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PERSPECTIVES


Laws and institutions must go hand in hand with the progress of the human mind. As that becomes more developed, more enlightened, as new discoveries are made, new truths disclosed, and manners and opinions change with the change of circumstances, institutions must advance also, and keep pace with the times. Thomas Jefferson, July 12, 1810 When the first federal legislation to prevent the misuse of genetic information was introduced in 1995, many in the health care, research, and policy communities considered the measure to be forward looking. Others called it premature. After all, scientists were just getting ready to . . .


The observations of finches that Charles Darwin made while in the Galapagos contributed to his theory of the origins of interspecies differences, ultimately leading to our understanding of mutation and natural selection as drivers of phenotypic variation. Now, more than 150 years later, genomewide association studies have identified more than 100 new chromosomal regions at which DNA variation influences risk of common human diseases and clinical phenotypes.1 Since previous approaches to identifying genetic causes of common diseases have met with very limited success, this moment constitutes a watershed in the history of genetics in medicine. Although associations with common single-nucleotide . . .


The far-reaching health care reforms that Massachusetts enacted in April 2006 are often cited as a model for other states.1 After 2 years, the good legislation to prevent the misuse of genetic information was introduced in 1995, many in the health care, research, and policy communities considered the measure to be forward looking. Others called it premature. After all, scientists were just getting ready to . . .


In 1987, an editorial accompanying a report on the use of high-dose interleukin-2 therapy for cancer asked whether the field of immunotherapy was at “the beginning of the end” or “the end of the beginning.”1 In retrospect, I would say it was at the “beginning of the beginning.” Have we made progress since then? Finn, in her review of tumor immunology in this issue of the Journal (pages 2704–2715), answers emphatically in the affirmative, and the report by Hunder et al., also in this issue (pages 2698–2703), underscores the remarkable potential of the immune system to eradicate cancer, even when . . .

ARTICLES


Progressive enlargement of the aortic root, leading to dissection, is the main cause of premature death in patients with Marfan’s syndrome. Recent data from mouse models of Marfan’s syndrome suggest that aortic-root enlargement is caused by excessive signaling by transforming growth factor â (TGF-â) that can be mitigated by treatment with TGF-â antagonists, including angiotensin II–receptor blockers (ARBs). We evaluated the clinical response to ARBs in pediatric patients with Marfan’s syndrome who had severe aortic-root enlargement. We identified 18 pediatric patients with Marfan’s syndrome who had been followed during 12 to 47 months of therapy with ARBs after other medical therapy had failed to prevent progressive aortic-root enlargement. The ARB was losartan in 17 patients and irbesartan in 1 patient. We evaluated the efficacy of ARB therapy by comparing the rates of change in aortic-root diameter before and after the initiation of treatment with ARBs. The mean (±SD) rate of change in aortic-root diameter decreased significantly from 3.54±2.87 mm per year during previous medical therapy to 0.46±0.62 mm per year during ARB therapy (P<0.001).

The deviation of aortic-root enlargement from normal, as expressed by the rate of change in z scores, was reduced by a mean difference of 1.47 z scores per year (95% confidence interval, 0.70 to 2.24; P<0.001) after the initiation of ARB therapy. The sinotubular junction, which is prone to dilation in Marfan’s syndrome as well, also showed a reduced rate of change in diameter during ARB therapy (P<0.05), whereas the distal ascending aorta, which does not normally become dilated in Marfan’s syndrome, was not affected by ARB therapy. In a small cohort study, the use of ARB therapy in patients with Marfan’s syndrome significantly slowed the rate of progressive aortic-root dilation.

Sudden death can occur as a consequence of cardiac-conduction abnormalities in the neuromuscular disease myotonic dystrophy type 1. The determinants of the risk of sudden death remain imprecise. We assessed whether the electrocardiogram (ECG) was useful in predicting sudden death in 406 adult patients with genetically confirmed myotonic dystrophy type 1. A patient was characterized as having a severe abnormality if the ECG had at least one of the following features: rhythm other than sinus, PR interval of 240 msec or more, QRS duration of 120 msec or more, or second-degree or third-degree atrioventricular block. Patients with severe abnormalities according to the entry ECG were older than patients without severe abnormalities, had more severe skeletal-muscle impairment, and were more likely to have heart failure, left ventricular systolic dysfunction, or atrial tachyarrhythmia. Such patients were more likely to receive a pacemaker or an implantable cardioverter–defibrillator during the follow-up period. During a mean follow-up period of 5.7 years, 81 patients died; there were 27 sudden deaths, 32 deaths from progressive neuromuscular respiratory failure, 5 nonsudden deaths from cardiac causes, and 17 deaths from other causes. Among the 17 patients who died suddenly in whom postcollapse rhythm was evaluated, a ventricular tachyarrhythmia was observed in 9. A severe ECG abnormality (relative risk, 3.30; 95% confidence interval [CI], 1.24 to 8.78) and a clinical diagnosis of atrial tachyarrhythmia (relative risk, 5.18; 95% CI, 2.28 to 11.77) were independent risk factors for sudden death.


We developed an in vitro method for isolating and expanding autologous CD4+ T-cell clones with specificity for the melanoma-associated antigen NY-ESO-1. We infused these cells into a patient with refractory metastatic melanoma who had not undergone any previous conditioning or cytokine treatment. We show that the transferred CD4+ T cells mediated a durable clinical remission and led to endogenous responses against melanoma antigens other than NY-ESO-1.


Dronedarone is a novel antiarrhythmic drug with electrophysiological properties that are similar to those of amiodarone, but it does not contain iodine and thus does not cause iodine-related adverse reactions. Therefore, it may be of value in the treatment of patients with heart failure. In a multicenter study with a double-blind design, we planned to randomly assign 1000 patients who were hospitalized with symptomatic heart failure and severe left ventricular systolic dysfunction to receive 400 mg of dronedarone twice a day or placebo. The primary end point was the composite of death from any cause or hospitalization for heart failure. After inclusion of 627 patients (310 in the dronedarone group and 317 in the placebo group), the trial was prematurely terminated for safety reasons, at the recommendation of the data and safety monitoring board, in accordance with the board’s predefined rules for termination of the study. During a median follow-up of 2 months, 25 patients in the dronedarone group (8.1%) and 12 patients in the placebo group (3.8%) died (hazard ratio in the dronedarone group, 2.13; 95% confidence interval [CI], 1.07 to 4.25; P=0.03). The excess mortality was predominantly related to worsening of heart failure — 10 deaths in the dronedarone group and 2 in the placebo group. The primary end point did not differ significantly between the two groups; there were 53 events in the dronedarone group (17.1%) and 40 events in the placebo group (12.6%) (hazard ratio, 1.38; 95% CI, 0.92 to 2.09; P=0.12). More increases in the creatinine concentration were reported as serious adverse events in the dronedarone group (8.1%) and 12 patients in the placebo group, 2.13; 95% confidence interval [CI], 1.07 to 4.25; P=0.03. The excess mortality was predominantly related to worsening of heart failure — 10 deaths in the dronedarone group and 2 in the placebo group. The primary end point did not differ significantly between the two groups; there were 53 events in the dronedarone group (17.1%) and 40 events in the placebo group (12.6%) (hazard ratio, 1.38; 95% CI, 0.92 to 2.09; P=0.12). More increases in the creatinine concentration were reported as serious adverse events in the dronedarone group than in the placebo group.


It is common practice to restore and maintain sinus rhythm in patients with atrial fibrillation and heart failure. This approach is based in part on data indicating that atrial fibrillation is a predictor of death in patients with heart failure and suggesting that the suppression of atrial fibrillation may favorably affect...
the outcome. However, the benefits and risks of this approach have not been adequately studied. We conducted a multicenter, randomized trial comparing the maintenance of sinus rhythm (rhythm control) with control of the ventricular rate (rate control) in patients with a left ventricular ejection fraction of 35% or less, symptoms of congestive heart failure, and a history of atrial fibrillation. The primary outcome was the time to death from cardiovascular causes. A total of 1376 patients were enrolled (682 in the rhythm-control group and 694 in the rate-control group) and were followed for a mean of 37 months. Of these patients, 182 (27%) in the rhythm-control group died from cardiovascular causes, as compared with 175 (25%) in the rate-control group (hazard ratio in the rhythm-control group, 1.06; 95% confidence interval, 0.86 to 1.30; P=0.59 by the log-rank test). Secondary outcomes were similar in the two groups, including death from any cause (32% in the rhythm-control group and 33% in the rate-control group), stroke (3% and 4%, respectively), worsening heart failure (28% and 31%), and the composite of death from cardiovascular causes, stroke, or worsening heart failure (43% and 46%). There were also no significant differences favoring either strategy in any predefined subgroup. In patients with atrial fibrillation and congestive heart failure, a routine strategy of rhythm control does not reduce the rate of death from cardiovascular causes, as compared with a rate-control strategy.

REVIEW ARTICLE


Major conceptual and technical advances in immunology over the past 25 years have led to a new understanding of cellular and molecular interplays between the immune system and a tumor. This review deals with important new concepts in antitumor immunity and their application to immunotherapy. The immune system can respond to cancer cells in two ways: by reacting against tumor-specific antigens (molecules that are unique to cancer cells) or against tumor-associated antigens (molecules that are expressed differently by cancer cells and normal cells). Immunity to carcinogen-induced tumors in mice is directed against the products of unique mutations of normal cellular.

SPECIAL ARTICLE


New developments in the search for susceptibility alleles in complex disorders provide support for the possibility of a polygenic approach to the prevention and treatment of common diseases. We examined the implications, both for individualized disease prevention and for public health policy, of findings concerning the risk of breast cancer that are based on common genetic variation. Our analysis suggests that the risk profile generated by the known, common, moderate-risk alleles does not provide sufficient discrimination to warrant individualized prevention. However, useful risk stratification may be possible in the context of programs for disease prevention in the general population. The clinical use of single, common, low-penetration genes is limited, but a few susceptibility alleles may distinguish women who are at high risk for breast cancer from those who are at low risk, particularly in the context of population screening.

IMAGES IN CLINICAL MEDICINE


A 35-year-old woman with bipolar disorder was found wandering on a highway screaming and crying, with disorganized speech. She was evaluated in the emergency department, and computed tomography of the head revealed a hypodense area. The patient reported that she had a nail in her uterus. In the context of the presentation, this was deemed to be unlikely. However, before magnetic resonance imaging was performed for further evaluation, radiography of the abdomen showed a large nail, which was localized to the bladder on ultrasonography, and an intrauterine device in the uterus. Surgery was scheduled to remove the nail, but on . . .


A 65-year-old woman with a history of hypertension and cigarette smoking presented with complete loss of vision in the inferior field of the left eye, which she had noticed an hour before presentation. She reported having had two transient episodes of amaurosis in the left eye the previous day. Visual acuity was 20/20 in both eyes. Dilated ophthalmoscopy of the left eye revealed a nonrefractile plaque in the proximal superior retinal artery (Panel A, arrow). Superficial retinal whitening in the superior macula signified retinal ischemia (Panel A, arrowheads). Fluorescein angiography showed delayed vascular filling in the superior retinal arteries . . .
CASE RECORDS OF THE MASSACHUSETTES GENERAL HOSPITAL


Dr. Allyson K. Bloom (Medicine): A 57-year-old woman was admitted to this hospital because of abdominal pain and weakness. One month earlier, a laparoscopic Roux-en-Y gastric bypass and cholecystectomy were performed for treatment of obesity and gallstones. Pathological examination of a liver-biopsy specimen revealed nonalcoholic fatty liver disease. The immediate postoperative course was uncomplicated, and she was discharged 2 days after surgery. At follow-up visits, she reported poor oral intake, episodes of tachycardia (which had occurred intermittently in the past), intermittent passage of watery stool and dark urine, and suprapubic and epigastric pain; on two occasions, fluids were administered intravenously . . .


Dr. Gregory K. Robbins (Infectious Diseases): A 63-year-old man was referred to the clinic for head and neck cancer, a multidisciplinary unit of this hospital, for management of cutaneous Merkel-cell carcinoma. He had been well until 3 months earlier, when he noted a small, painless nodule on the superior, right-central aspect of his forehead. During the next 3 weeks, this nodule grew slowly, and a second, pea-size, painless nodule developed in front of his right ear. Pathological examination of a biopsy specimen of the lesion on the forehead indicated a small-cell carcinoma that was thought to be consistent with Merkel-cell . . .

CLINICAL PRACTICES


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 previously well 42-year-old woman presents with severe pain in the right upper quadrant, which started 15 hours earlier. She has previously noted episodic pain in that location that lasted for up to 2 hours but has not sought medical advice. She has had one episode of vomiting with the current attack. On physical examination, her temperature is 38.5°C, and the heart . . .


Femoral venous catheterization is a rapid way to obtain intravenous access in hospitalized or emergency department patients. In this video, you will learn how to safely place a femoral line. Placement of a femoral line may be indicated in the following situations: to obtain vascular access when peripheral access cannot be accomplished, to administer hemodialysis when access at a preferable site is not an option, to perform cardiac catheterization, or to administer large or caustic infusions. The following situations are relative contraindications: an uncooperative patient; the presence of infection, trauma, or distorted anatomy at the insertion site; . . .

IMAGES IN CLINICAL MEDICINE


A 71-year-old woman received a diagnosis of systemic sclerosis more than 30 years ago when she presented with Raynaud’s phenomenon and cutaneous sclerosis. At that time she did not require long-term therapy. She now presents with fever and venous ulceration of both legs. On physical examination it was discovered that the tips of all 10 fingers and some toes were missing. She reported no history of severe trauma or surgery to her fingers or toes. A test for antinuclear antibodies was positive at 1:1280, and though unusual, there were detectable levels of both anti-Scl70 antibodies and anticentromere antibodies; the presence . . .


A 28-year-old man with idiopathic dilated cardiomyopathy who had had St. Jude aortic- and mitral-valve replacements 3 years earlier presented with decompensated heart failure. The examination was notable for marked jugular venous distention, an S3 gallop, and a palpable left ventricular heave. The carotid upstrokes were normal, but the prosthetic second heart sound was diminished. A grade 2/6 systolic murmur was audible at the right upper sternal border. The international normalized ratio was 3.0 and had been within the therapeutic range consistently over the previous months. Valve fluoroscopy confirmed immobilization of one of the mechanical aortic-valve leaflets, consistent with obstruction . . .

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