SUPERBUGS

Elsewhere in this issue, Dr. Cristie Columbus talks about the emergence of disease-causing bacteria that are resistant to our most powerful antibiotics, and recently an article by Sheryl Cay Stolberg (1) on this subject appeared in the New York Times Magazine. While popular movies have appeared about the Ebola virus, the big danger lies in the common microorganisms that have developed resistance to commonly used antibiotics. The list of dangerously virulent, drug-resistant microbes has been growing, of course, in recent years: *Streptococcus pneumoniae*, *Mycobacterium tuberculosis*, and *Neisseria gonorrhoeae*, but none of these are as frightening as the VISA strains of staphylococcus. VISA stands for vancomycin intermediate-resistant *Staphylococcus aureus*. Within the past 18 months, the Centers for Disease Control and Prevention in Atlanta has documented the first 4 cases ever. Their emergence is an ominous harbinger of what could be an infectious disease disaster.

The major reason for concern, of course, is that staphylococcus is present normally in the skin and nostrils as part of the normal flora. It is harmless there, but when it gains access to the interior, the organism can be dangerous. Should VISA strains become common, simple cuts and scrapes could become mortal wounds. It is estimated that each year in the USA nearly 90,000 patients die of a hospital-acquired infection, and *Staphylococcus* species often is the culprit. The emergence of an untreated strain of *Staphylococcus* species would put virtually any healthy person at risk. Meanwhile, drug manufacturers, that in the early 1980s all but abandoned development of new antibiotics on the theory that they were no longer needed, find themselves behind the curve; they are hustling to invent new antibiotics, and that is why the emergence of the vancomycin-resistant strains is viewed as such a worrisome public health threat.

The next generation of new antimicrobials is, by the industry’s own estimate, at least several years away, creating a dangerous window in which the virulent new microbes might be able to spread unchecked. If that happens, modern medicine might revert to the days before penicillin, when sore throats could become fatal, and patients who walked into hospitals for routine surgery might be carried out in coffins.

Penicillin was introduced in 1943. It was available initially without a prescription, and consumers gobbled it up like candy. Within 3 years of its introduction, however, mutant forms of bacteria began to resist the new miracle drug. By 1946, only 3 years after penicillin’s introduction, an estimated 15% of *Staphylococcus* strains isolated from patients, in a single London hospital at least, had developed resistance to penicillin. In the 3 decades following the introduction of penicillin, new microbe killers were discovered, tested, and approved for marketing at a phenomenal pace -- streptomycin, erythromycin, tetracycline,
and amoxicillin. By the 1970s, the common wisdom was that the battle of the bugs versus the drugs was over. With more than 100 antibiotics available, the government de-emphasized bacterial research, and the drug industry, sensing a saturated market, shifted resources elsewhere. Bacteriology was passé.

In May 1998, the Institute of Medicine complained that no nation, including the USA, had an adequate system for monitoring the emergence of these drug-resistant microorganisms. Despite public education campaigns, physicians, sometimes pressured by patients, prescribe unnecessary drugs. Possibly 20% to 50% of the 145,000,000 prescriptions given each year to outpatients in the USA are unnecessary, as are 25% to 45% of the 190,000,000 annual doses of antibiotics delivered in the hospital.

In the microbial world, where only the fittest survive, some microorganisms stumble upon genetic mutations that protect them from the drugs. In the presence of antibiotics, the weak organisms—those that lack these mutations—die off, leaving only the strong ones to survive and proliferate. The more antibiotics are used and misused, the more the drug-resistant bugs appear. The net effect of all of this activity is clear: many germs are becoming resistant not only to 1 drug but to 6 and 7 drugs. The story of multidrug-resistant tuberculosis is now well known. Less familiar is the fact, reported by the Institute of Medicine, that >90% of Staphylococcus aureus strains are now resistant to penicillin and a wide variety of other antibiotics, including methicillin, the drug that is next to last in the line of defense before vancomycin. In 1995, in New York City alone, methicillin-resistant Staphylococcus infections killed 1409 people, 200 more than were murdered in that city that year.

As resistance to each antibiotic continued to develop in the mid-1980s, infectious disease experts have been waiting and watching for the last domino to fall: the emergence of Staphylococcus species that are resistant to vancomycin. Some experts have predicted complete resistance of Staphylococcus to vancomycin by the end of this decade which, of course, is <15 months away. Drug companies are now pouring hundreds of millions of dollars into new antibiotics; as of 1996, there were at least 27 new microbe killers in the development pipeline. The mission of the drug companies is to create an entirely new antibiotic, one that kills microbes using mechanisms that are different from those already on the market. The most promising candidates seem to be linezolid and Ziracin, but bringing a new class of antibiotics to market will take time; even the front-runners are not expected to be approved until at least year 2000 or 2001. In the meantime, another drug, Synercid, is hoped to fill the gap. It is on the verge of receiving approval from the Food and Drug Administration, and it is the first injectable form of a class of antibiotics called streptogramins. It was not developed, however, to combat vancomycin-resistant Staphylococci, but it appears to work against VISA strains in the laboratory.

As the race to find new drugs proceeds, supermicrobes will undoubtedly continue to flourish, leaving a trail of nervous public health officials and grieving families in their wake.
THE TWENTIETH CENTURY’S FINEST MEDICAL DISCOVERY: PENICILLIN

Recently I had the privilege of interviewing Dr. David C. Sabiston, Jr., the longtime chairman of the Department of Surgery at Duke University Medical Center, the editor of *Textbook of Surgery*, and the coeditor of *Surgery of the Chest* (2). In 1962, Dr. Sabiston did the first coronary bypass operation. In 1958, Dr. Sabiston’s chief at The Johns Hopkins Hospital, Dr. Alfred Blalock, encouraged him to spend a sabbatical year doing experimental work in atherosclerosis with Dr. Howard W. Florey, who was chairman of the Department of Pathology at Oxford University in the United Kingdom. I had known of Dr. Florey’s work with penicillin but had not known that his last years were spent studying atherosclerosis.

The August 17-24, 1998, issue of the *U.S. News & World Report* had a long piece on the great inventions of the twentieth century. The story of penicillin started with Fleming in 1922 and continued with Florey and Chain 13 years later. Fleming, who had a cold, sneezed on a culture plate (3). He observed that when bacteria later formed on the plate, none developed in the spots of mucus. Thus, Fleming discovered lysozyme -- a substance found in body fluids and body tissues that dissolves bacteria. He thought at the time that it might be the key to a potent natural antiseptic, but tests showed that it acted only against harmless organisms, and Fleming consequently lost interest. In 1928, serendipity hit Fleming again. A mysterious mold sprouted on a discarded culture plate that had gone unwashed for 2 weeks while he was on holiday. Once again Fleming observed antibacterial action -- bacteria covered all of the plate except where the mold was. This time the bacteria were *Staphylococci* species. The mold juice also proved able to retard the growth of many other kinds of virulent bacteria. Fleming chose the name *penicillin* for this natural antiseptic after identifying the mold as a type of *Penicillium*. Fleming had long sought a potent germicide for dabbing on wounds, but his enthusiasm soon cooled after more tests showed that penicillin was slow acting and hard to produce in quantity. He wrote up his findings, however, in a 1929 article that was met with yawns. Fleming had presented penicillin as a possible antiseptic and nothing more. He made no attempt to test its therapeutic potential when given systemically. He did inject the mold broth filtrate into a healthy rabbit and a healthy mouse to test for toxicity, but he did not give it to diseased animals. Had he done so, the “miracle drug” might have appeared a decade sooner.

In 1935, Howard Florey became head of Oxford’s new Sir William Dunn School of Pathology. He recruited a young Cambridge PhD in biochemistry named Ernest Chain, a Jewish refugee from Hitler’s Berlin. The Australian-born Florey and the German-born Chain, although longtime collaborators and later cowinners of the Nobel Prize with Fleming, developed such a dislike for each other that they ended up communicating only by memo. Nevertheless, seeking the magic bullet against infectious disease, Florey and Chain found themselves investigating Fleming’s serendipitous discoveries. They purified lysozyme and identified it as an enzyme. Even when purified, however, it proved clinically worthless.

Fleming’s 1929 paper on penicillin left many unanswered questions. The Oxford team took up where Fleming left off, beginning years of painstaking work. In May 1940, Florey and
Chain injected 4 of 8 bacteria-infected mice with penicillin (1 with only a weak dose) and left 4 untreated. The untreated mice and the mouse given a weak dose died. The 3 receiving larger doses of penicillin survived. With the Depression on and World War II soon to start, Florey and Chain had trouble getting research money to support their penicillin research. Their first grant was for $125.00. Florey appealed to the Rockefeller Foundation in the USA, and it provided support. The only commodity in shorter supply than money was penicillin. The Oxford team was growing the mold in every receptacle it could get—from china plates to bedpans—but the yield of injectable material was frustratingly low. In one of the first human trials, the patient exhausted the team’s entire supply of penicillin, and then the patient died when therapy ceased.

In mid-1941, Florey flew to the USA to attempt to sell the US government and US drug companies on penicillin’s potential. Before long, many laboratories were producing penicillin. By June 1944, when the Allies invaded France, large supplies of the yellow liquid were on hand, saving countless lives during the rest of the war. Infection from wounds, which in previous wars had killed many more men than bullets had killed, suddenly was survivable; when treated with penicillin, 95% of the wounded survived.

Fleming had no role in any of this until very late. After the Oxford team published its first paper on penicillin in 1940, Fleming asked Florey if he could visit the Dunn School. Chain was astonished: “Fleming? Good God, I thought he was dead.” When Fleming arrived, he said, “I have come to see what you have been doing with my old penicillin.” He said little else, apparently, during the tour and was not seen again for 2 years, when he phoned to request penicillin for a friend desperately ill with meningitis. Florey supplied it along with instructions for administering it. The patient recovered, and Fleming, at last, became a believer in his discarded discovery; he launched a heartfelt, if belated, personal campaign for mass production.

When the media realized that penicillin was indeed a magical bullet, the press descended on both Fleming and Florey. Fleming readily gave interviews and happily posed for photographers in his laboratory among his Petri dishes; Florey, never one to suffer fools gladly, had a deep aversion to publicity. When reporters arrived at the Dunn School, he ducked out the back door. Few public relations boners in the history of science have been so fateful. The press thereafter presented Fleming as the solitary genius behind penicillin. The Oxford team was either not mentioned at all or relegated to a few lines. Fleming, in his speeches, however, always gave credit to Florey and Chain, who had purified penicillin chemically, and their associates for their work. He adopted a charmingly self-deprecating stance. “I did not invent penicillin,” he would say. “Nature did that. I only discovered it by accident.” Fleming, however, never confessed to how clueless he had been for more than a decade about his own find.

Although the wise Nobel committee gave the 1945 Medicine Prize to Fleming, Florey, and Chain, Florey and Chain continued to get short shrift in public print. The plainspoken Florey, fuming in private, always held his tongue in public.

Alexander Fleming died in 1955 at age 74. Revisionist biographers and historians in time pieced together the true story of penicillin’s development. Nevertheless, at the century’s
end, much of the Fleming myth was still enshrined in *Encyclopedia Britannica*.

Howard Florey, with whom David Sabiston worked for 1 year, shifted his research from penicillin to atherosclerosis after World War II. Sabiston confided that during his year with Florey, Florey had developed angina. When Sabiston returned to Baltimore, with Blalock’s urging, he began making plans to do coronary endarterectomy and possibly coronary bypass. Unfortunately, the operation had not been developed before Florey’s angina caused his death back at Oxford.

**WE THINK WE ARE ONE, WE ACT AS IF WE ARE ONE, BUT WE ARE NOT ONE (4)**

Natural carnivores live on meat. Natural herbivores live on vegetables, fruits, and starches (rice, corn, potatoes, beans, pasta). Carnivores and herbivores are made differently (*Table 1*). Carnivores have claws and sharp teeth for ripping meat apart; herbivores have hands (unless they have hooves) for gathering food and flat teeth for grinding the vegetables, fruits, and grains. Carnivores have short bowels, rapidly digest flesh, and rapidly excrete the putrefying animal products. The time required for food to travel through their intestinal tract is short. Herbivores have long intestines so that there is plenty of time to digest the nutrients in the plants, fruits, and starches, and when these animals eat these foods, their transient times also are relatively short, despite their long intestinal tracts. Meat eaters pant to cool themselves and lap water; plant eaters, in contrast, sweat to cool and sip water. Carnivores synthesize their own vitamin C, which is virtually absent in meat and dairy products; herbivores obtain their vitamin C from plant foods in which it is abundant.

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<td>Appendages</td>
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Although human beings eat meat, we are not natural carnivores. We were intended to eat plants, fruits, and starches! No matter how much fat carnivores eat, they do not develop atherosclerosis. It is virtually impossible, for example, to produce atherosclerosis in a dog, even when 100 grams of cholesterol and 120 grams of butter fat are added to its meat ration (5). (This amount of cholesterol is approximately 200 times the average amount that human beings in the USA eat each day!) In contrast, herbivores rapidly develop atherosclerosis if they are fed foods, namely fat and cholesterol, intended for natural carnivores. Adding only 2 grams of cholesterol daily for 2 months to a rabbit’s chow, for example, produces striking fatty changes in its arteries. And humans are like rabbits, natural herbivores, not like dogs or cats, natural carnivores.
Thus, although we think we are one and we act as if we are one, human beings are not natural carnivores. When we kill animals to eat them, they end up killing us because their flesh, which contains cholesterol and saturated fat, was never intended for human beings, who are natural herbivores.

**SHIFTING FROM DECREASING RISK TO ACTUALLY PREVENTING AND ARRESTING ATHEROSCLEROSIS — THE GOAL: A 2-DIGIT, LOW-DENSITY LIPOPROTEIN CHOLESTEROL**

The higher the serum low-density lipoprotein (LDL) cholesterol, the higher the frequency of symptoms of organ or tissue ischemia, the higher the frequency of death from consequences of atherosclerosis, and the greater the quantity of the atherosclerotic plaques at necropsy. A number of studies in humans point toward a threshold LDL cholesterol number, below which atherosclerotic plaques do not form and above which atherosclerotic plaques do form. Evidence points toward that threshold LDL cholesterol number as 100 mg/dL. At this LDL cholesterol number, the serum total cholesterol is usually about 150 mg/dL.

Assuming the correctness of this threshold LDL cholesterol number, guidelines for treatment of both primary and secondary (previous atherosclerotic event) prevention could be greatly simplified, the goal being LDL cholesterol <100 mg/dL, irrespective of the presence or absence of other atherosclerotic risk factors and irrespective of whether an atherosclerotic event had occurred previously.

Is it realistic to talk in terms of the ideal rather than in terms of the obtainable, the present guidelines of which are an example? The present treatment guidelines for patients with hypercholesterolemia focus, of course, on the LDL cholesterol number plus whether or not other risk factors (age, systemic hypertension, cigarette smoking, diabetes mellitus, high-density lipoprotein cholesterol <35 mg/dL) are present and whether an atherosclerotic event has occurred. If the LDL is >190 mg/dL without other atherosclerotic risk factors, the goal is 160 mg/dL. If the LDL is >160 mg/dL with other risk factors but without an atherosclerotic event, the goal is LDL <130 mg/dL. If the LDL is >130 mg/dL and an atherosclerotic event has occurred, irrespective of the presence or absence of other risk factors, then the LDL goal is <100 mg/dL. I have never understood the viewpoint that it is good to have an LDL cholesterol <100 mg/dL after an atherosclerotic event, when surely it must be better to have an LDL <100 mg/dL before an atherosclerotic event (and then we probably would not have to worry about having an event). The average LDL cholesterol in persons with an atherosclerotic event is about 140 mg/dL.

The argument that most adults in the USA cannot afford therapy necessary to lower the LDL cholesterol to <100 mg/dL simply does not hold, because the least expensive diet is the vegetarian one, and the average LDL cholesterol is <100 mg/dL in chronic vegetarians. Now I am not naive enough to believe that most Americans suddenly will switch from a flesh diet to a vegetable-and-fruit diet to prevent atherosclerosis, but the point is that the least expensive diet is the vegetarian one, and as long as we do not use highly saturated vegetable oils such as coconut oil or palm kernel oil, it is the one that when adhered to over
decades is essentially unassociated with atherosclerosis.

Because most of us are not willing to become vegans or ovo-lacto vegetarians—we love the cooked muscle of cows, pigs, chickens, and turkeys too much—many of us will require the cholesterol-lowering drugs, which indeed are effective no matter what we eat, for us to achieve the threshold LDL cholesterol number of $<100\text{ mg/dL}$. The more drug we take, the greater the expense. The more meat we eat, the greater the expense of our diet. Some type of compromise between diet and drugs would save money and prevent plaques. With 21 meals weekly, we might limit our flesh consumption to only 7 meals a week. This regimen would not require that we never “pig out” on occasion but that the total calories, grams of cholesterol, and grams of saturated fat consumed during the entire week be compatible with an LDL cholesterol $<100\text{ mg/dL}$, which also generally means that maintenance of an ideal body weight is necessary to achieve the threshold LDL cholesterol goal.

STEAD AND BEESON

Eugene A. Stead, Jr., and Paul B. Beeson have been 2 of the most renowned internists in the USA this century. One a cardiologist and the other an infectious disease specialist, each became chairman of the Department of Medicine at Emory University School of Medicine in Atlanta. In 1946, Stead went from there to be chairman of Medicine at Duke and, in 1952, Beeson went from there to chair the Department of Medicine at Yale. Their impact on their trainees has been enormous. Wagner and colleagues wrote a book titled *E. A. Stead, Jr.: What This Patient Needs is a Doctor*, and this book demonstrates the reasons his impact has been so strong (6). The summer 1998 issue of *The Pharos* carried a piece titled “Character is Fate: The Life of Paul B. Beeson,” which provides details I had not heard previously (7).

My father, a professor of Medicine at Emory, taught Stead as a medical student at Emory. Stead was born in Atlanta, Georgia, in 1908, and Beeson was born the same year in Livingston, Montana, and spent his childhood in Livingston, Seattle, and Anchorage. In August 1957, I took a bus from Atlanta to the Northeast to visit a number of prominent hospitals. I remember walking into Dr. Beeson’s office one hot summer afternoon in New Haven while he was chairman of Medicine. He graciously invited me into his office. I told him that I was looking for an internship. He showed me around the medical wards at Grace New Haven Hospital and spent about an hour with me. A kinder man I had never met, and I was a coatless and tieless 24-year-old just about to begin my senior year in medical school. Recently, I viewed a video in the series *Leaders in American Medicine* sponsored by Alpha Omega Alpha and titled *Eugene Stead: A Conversation With Paul Beeson*. The following are notes I made while viewing that video:

When Stead was chief resident in medicine at Cincinnati General, Dr. Soma Weiss from Harvard came to Cincinnati as a visiting professor in January 1937. Weiss was there for about 3 days, and Stead and Weiss apparently hit it off quite well. Weiss offered Stead a position as a clinical investigator at the Thorndike Laboratory at Boston City Hospital beginning in July 1937. Weiss offered Stead a $900.00 annual salary. Stead indicated to Weiss that he would need $1800.00 to come to Boston. Weiss initially said “no.” Stead told Weiss that if he found $900.00 more during the next 5 months, he would like to come to the
Thorndike. In April 1937, Weiss wired Stead that he had found $900.00 more and Stead accepted the position. Stead had been with Soma Weiss for 2 years at the Thorndike when Weiss accepted the chairmanship of the Medicine Department at the Peter Bent Brigham Hospital. Stead moved to the Brigham with Weiss. At the time that Weiss and Stead moved to the Brigham, Paul Beeson was chief resident in medicine there.

Both Stead and Beeson considered Weiss a great man, primarily because of his enormous effect on other people. Weiss was sincerely interested in each of his trainees, a great catalyst for young people. Weiss seemed to make the day “lighter” for all those around him. His ability to inspire was his greatest attribute in the views of Stead and Beeson. Weiss got the very best out of everyone he touched. He did not make particularly brilliant diagnoses, although he was a sound physician. He had a unique ability to focus on the problem. He was also willing to give considerable responsibility to very young people. It was his personal qualities, however, that dominated. He thus produced an atmosphere where there was relatively little difference between work and play. Work was enormously exciting. In the late 1930s and early 1940s, young trainee physicians were not married. They all lived in the hospital. It was sort of a club of young men. Weiss was fluent in German and read not only English medical literature but German literature as well. This German fluency allowed Weiss to be a notch ahead of those who read only English medical literature. The work on reflex control of the circulation, for example, was initiated by an article that Weiss had read in a German medical journal.

In the fall of 1941, Stead volunteered to join a combined Harvard-Duke physician unit in the reserves of one of the armed services. Shortly thereafter, he was offered the chairmanship of the Department of Medicine at Emory. He was offered an annual salary of $6000.00. He told those at Emory who offered him the position that he needed $8000.00 annually to come. Finally, Emory came up with the additional $2000.00, and he accepted the position. Stead was the second full-time faculty member at Emory University School of Medicine. When he became chairman, the total budget of the Department of Medicine was $23,500.00, and that included the salaries of Stead, the secretary, and the young associates. When Stead received the offer at Emory, Soma Weiss was the only Harvard faculty member in Boston who advised him to go. Weiss told Stead that to have his own department was the only way for him to find out how good he was. Emory insisted that if Stead accepted the Emory chairmanship, he would not be permitted to volunteer to serve in the armed services. Stead accepted the position in November 1941 and was released from the Harvard-Duke unit.

Not long before Stead left Boston, he married Evelyn, who was Soma Weiss’ secretary. The wedding occurred in Soma Weiss’ home. They were married on Saturday, and Soma Weiss gave Stead time off on Saturday, Sunday, Monday, and Tuesday for a honeymoon. He was back at work on Wednesday.

Shortly after Stead accepted the position at Emory, Soma Weiss died suddenly at age 42 (ruptured intracerebral aneurysm), and from the time of Weiss’ death until Stead went to Emory, Stead was acting chief of the Department of Medicine at the Peter Bent Brigham Hospital.

When Stead arrived at Emory he was professor of Medicine but not chief of any of the
medical services. At Grady Hospital there was a chief of Medicine of the black service and a chief of Medicine of the white service. (Both of those medical services at the time, of course, were separate.) These chiefs of service were at the hospital for only about an hour a day. Because Stead was there all day, he, in essence, was chief of both services. What Stead said he learned from this was that titles don’t mean much. It is performance that counts.

When Stead went to Emory he took several young faculty with him, including Jim Warren. Paul Beeson was in England at the time, and Stead also offered him a job. Beeson, who married in July 1942, had also tentatively received an offer from Dr. Barr at Cornell for $4500.00 a year. Stead offered Beeson $4000.00 to come to Emory. Stead put a deadline on the offer, and at the time of the deadline, Cornell had not given Beeson a firm offer, and, therefore, Beeson went to Atlanta. When Beeson arrived in Atlanta, Stead had already set up a laboratory for him and provided him with a technician. They had not discussed that before Beeson came to Emory. Beeson immediately took charge of the bacteriology laboratory at Emory, and he liked that very much because he saw from reading the blood culture agar plates daily where all the problems were in the hospital. Soon, the medical residents were rotating through his bacteriology laboratory. Stead held Grand Rounds every Sunday morning at Grady. Stead later got Bob Grant and Jack Myers to come to Emory.

Not long after Beeson arrived at Emory he became the local penicillin czar. They had a patient with active infective endocarditis, and at that time Chester Keefer (Boston) was the national penicillin czar. Late one evening, a reporter called Stead and asked him if he was going to call Chester Keefer to get some penicillin for a particular patient at Grady Hospital. Stead told the reporter that he would call Keefer the next morning. The reporter said if he waited until the next morning to call Boston, his newspaper would publish a story to the effect that the chairman of Medicine at Grady Memorial Hospital was unwilling to call Chester Keefer to have penicillin sent for this young man with infective endocarditis. As a consequence, Stead called Chester Keefer at 1:00 AM. Keefer was enormously annoyed but, nevertheless, sent the penicillin to Atlanta, and the young man survived.

Not long after Stead arrived at Emory he began looking for contracts from the government to get money to retain staff and to do research. The federal government at that time had money for research primarily in 2 areas: 1) shock and 2) syphilis. At first Stead thought work on syphilis would be most useful, but Jim Warren urged him to work on shock instead. Stead agreed and sent Warren to New York to learn how to do cardiac catheterizations with Dick Richards and Andre Cournard. When Jim Warren returned to Atlanta, he and Stead decided to study shock patients on Friday night, Saturday night, and Sunday. Shock patients, however, were not always readily available, and when they weren’t, the doctors studied patients in congestive heart failure. They started putting catheters everywhere in the body. Paul Beeson also participated in doing a number of cardiac catheterizations. Beeson got interested in determining whether arterial blood or venous blood contained more microorganisms in patients with septicemia. He also learned that the hepatic vein, which he catheterized for the first time, was devoid of microorganisms when they were present in other blood vessels in the body.

The forward flow theory of congestive heart failure, of course, was worked out by Stead and Warren. Stead described congestive heart failure as not putting out enough water by the kidneys. If there was lots of rain and a poor drainage system, water would accumulate and,
in the human body, it would accumulate in the bloodstream and in the tissues. Stead indicated that the basic cause of heart failure was a drainage system that was stopped up when the rain continued. At that time, the only type of diuretic was an injectable one. Oral diuretics came later. So therapy for heart failure at that time boiled down to dietary restriction of salt.

When Stead and Warren were working on congestive heart failure, Bill Stead, Eugene’s brother, was an intern and assistant resident in medicine. A patient came in with jaundice, and he presented that patient to Eugene Stead, who was taking morning report. Bill Stead had indicated that 2 months earlier the patient had been hospitalized for a burn. Eugene Stead thought that the burn had nothing to do with the patient’s present jaundice. Then Bill Stead went to see Beeson. Beeson had recalled that when he was in England a number of servicemen became jaundiced after receiving yellow fever vaccine. It turned out that the yellow fever vaccine contained some serum. Beeson also learned that the patient, who was admitted by Bill Stead, had received a blood transfusion during the burn treatment 2 months earlier. What grew out of that scenario was the first report on serum hepatitis following blood transfusions. This was a major work, which the *Journal of the American Medical Association* quickly published.

Eventually, enough penicillin became available to treat most patients who had active infective endocarditis. A patient at Grady had active infective endocarditis and severe congestive heart failure. The patient was treated and the infection was cured, but several months later, heart failure killed the patient. This was the first time it was realized that curing the infection was not enough; if the valvular damage had already produced such a leaky valve, heart failure was the consequence.

In 1946, Stead was offered the chairmanship of the Department of Medicine at Duke University Medical Center in Durham, and he found the position quite attractive. He enjoyed Emory and Grady very much and actually hated to leave, but he thought his opportunities at Duke were greater than those at Emory. He viewed the Duke situation better than the Emory one, primarily for 3 reasons. 1) Duke had the ready availability of private patients for teaching. Stead believed that the best training for young physicians was to take care of both public and private patients, not exclusively public patients. He indicated that the physicians who had trained in medicine at Grady and then went into private practice always loved coming back to Grady to make teaching ward rounds because they saw more interesting illnesses than in private practice. 2) Stead had become dean of the medical school at Emory. He did not like being the dean, but he thought it would be difficult to give it up. He wanted to go back to the medical wards and limit himself to medicine. He felt that even if he gave up the deanship at Emory, many individuals would keep coming to him because of the power and insight he had accumulated for himself at Emory. 3) He thought the financial situation, not only for himself but also for the Department of Medicine, was more favorable at Duke than at Emory. There were many faculty at Duke who were essentially in private practice but contributed some of their fees to the medical staff. Therefore, there was more flexible money available at Duke than at Emory at the time. At Duke he figured that if a physician wanted to be purely an academician, that would be fine, but the physician’s income would be less than that of one who wanted to practice full-time. Both types of physicians would be in the department, however.
Beeson followed Stead as chairman of the Department of Medicine at Emory, and Beeson remained chairman for 6 years until he went to Yale in 1952. Many of the young faculty that Stead had gathered at Emory went to Duke with him. Beeson indicated that he counted the number of Stead trainees who subsequently became chairmen of various departments of medicine in the USA, and that number was 17 or 18. When Stead was at Emory, the housestaff and the young faculty essentially worked around the clock. It was Stead’s belief that either you worked around the clock at Grady or you joined the armed services. One of Stead’s famous quotes was: “If you can’t get your work done in 24 hours, you should work at night.”

Stead stated that when he went to Duke he found it more a country club–type atmosphere than Emory. He rapidly converted Duke’s medical center physicians into the hardest working medical houseofficers in the country, and his housestaff rapidly developed a reputation to that effect. Stead considered himself always to be “performance oriented.” He favored taking less bright individuals who really wanted to do something rather than taking brighter individuals who were a bit lazy. He was determined to take only those who really wanted to work. The housestaff at Duke lived in the hospital, even those who were married. For the young housestaff who stayed as faculty, Stead tried to provide protected time for them so that they could get their research going. He considered his program a self-selection process. Those who did best during the houseofficer period were the ones who stayed on the faculty. The Duke formula, which made for a stable financial situation, apparently was followed by a number of other medical centers later on.

**LIFE SPAN AND INCOME GO TOGETHER**

A governmental report titled *Health, United States, 1998* (8) indicated that people in the USA now live an average of 76.1 years and that the gaps in longevity between the genders and races have narrowed. There was strong evidence that life span is related to income. The near-poor are, on average, healthier than those living in poverty; middle-income people are healthier than the near-poor; and people with high incomes tend to be the healthiest.

Education also lengthens life and enhances health. Less-educated adults had higher death rates for all major causes of death, including chronic diseases, infectious diseases, and injuries, compared with more-educated adults. Education also governed smoking habits. Between 1994 and 1995, cigarette smoking declined among adults aged 25 and over: the declines were greatest among the best educated; the least educated were more than twice as likely to smoke as were people with more education. Thus, good education and good income lead to good health.

The infant death rate has declined to an all-time low of 7.3 deaths per 1000 births in 1996. Heart disease continues to decline, down 12% from 1990 to 1996. During the same period, deaths from cancer dropped by 5%, halting its steady climb for the first time.

**HEAT STROKE IN CHICAGO**

The extremely hot weather in Dallas in the summer of 1998 makes an article on near-fatal heat stroke during the 1995 heat wave in Chicago a bit more pertinent than otherwise (9). From July 12 to July 20, 1995, Chicago sustained a heat wave that resulted in >600 excess deaths and 3300 excess emergency department visits. Daily temperatures during that time
ranged from 33.9°C (93°F) to 40.0°C (104°F), and on July 13, the heat index peaked at 48.3°C (119°F). The maximum number of emergency department visits occurred 24 hours later. The medical examiners office reported the peak number of deaths on July 15, and that was also the day of peak admissions to area intensive care units. Critically ill persons were admitted with classic heat stroke, defined by a body temperature >40.6°C (>105°F) in the presence of altered mental status and anhidrosis.

Heat stroke has been classified as exertional or classic. Exertional heat stroke is precipitated by heavy exertion in very hot and humid climates and usually is seen in otherwise healthy young persons. Classic heat stroke results from unabated exposure to high temperatures and humidity. Elderly persons with premorbid conditions are likely to experience classic heat stroke. Surprisingly, reports on clinical features of classic heat stroke are rather limited.

Of 58 patients admitted to Chicago hospitals from July 12 to July 20, 1995, with classic heat stroke, 100% had multiorgan dysfunction with neurologic impairment, 53% had moderate-to-severe renal insufficiency, 45% had disseminated intravascular coagulation, 10% had acute respiratory distress syndrome, and 57% had evidence of infection on admission. In-hospital mortality was 21%. Many survivors became disabled; 33% of the patients had moderate-to-severe functional impairment at hospital discharge. After 1 year, no patient had improved functional status, and an additional 28% of the patients had died. These patients averaged 68 years of age; the numbers of men and women were nearly equal; and blacks comprised 64%, whites 28%, and Hispanics nearly 9%. Thus, it appears that persons who have sufficient quantities of money to afford air conditioners are not candidates for classic heat stroke. This is another example of how economics often determine health.

ALENDRONATE FOR THE PREVENTION AND TREATMENT OF GLUCOCORTICOID-INDUCED OSTEOPOROSIS

Osteoporosis, perhaps the most debilitating complication of long-term corticosteroid therapy, leads to bone loss that ultimately leads to fractures in up to 50% of patients. Estrogen, vitamin D, and calcitonin prevent bone loss in some but not all patients treated with glucocorticoids. Recently, bisphosphonates have been used for glucocorticoid-induced osteoporosis because of their ability to inhibit bone resorption and their relatively few side effects.

Alendronate is a potent bisphosphonate that increases the bone mineral density of the hip, spine, and total body, and lowers the incidence of vertebral, hip, and forearm fractures by approximately 50% in postmenopausal women with osteoporosis. Saag and associates (10) for the Glucocorticoid-Induced Osteoporosis Intervention Study Group carried out 2 randomized, 48-week trials using 2 doses of alendronate in 477 men and women 17 to 83 years of age who were receiving glucocorticoid therapy. The mean bone density of the lumbar spine increased by 2.1% and 2.9%, respectively, in the groups that received 5 mg and 10 mg of alendronate per day, and decreased by 0.4% in the placebo group. The femoral neck bone density increased by 1.2% and 1.0% in the respective alendronate groups and decreased by 1.2% in the placebo group. The bone density of the trochanter and total body also increased significantly in the patients treated with alendronate. Furthermore, there
were fewer new vertebral fractures in the alendronate group (overall incidence = 2.3%) than in the placebo group (3.7%). Thus, alendronate increases bone density in patients receiving glucocorticoid therapy and lowers the frequency of fractures.

EFFECTS OF CLODRONATE TREATMENT ON NEW BONE METASTASES IN PATIENTS WITH BREAST CANCER AND TUMOR CELLS IN BONE MARROW

Bisphosphonates inhibit osteoclast-mediated bone resorption by mechanisms that are not fully understood. In patients with breast cancer and bone metastases, bisphosphonates have been demonstrated to reduce the incidence of hypercalcemia, bone pain, and pathologic fractures, but overall survival has not been prolonged. Most recently, Diel and associates (11) from Heidelberg and Frankfurt, Germany, evaluated the effects of oral clodronate in patients with primary breast cancer and tumor cells in bone marrow: 157 received clodronate, 1600 mg/day orally for 2 years. Distant metastases were detected in 21 (13%) of the 157 patients in the clodronate group and in 42 (29%) of the 145 control subjects. The frequency of both osseous and visceral metastases was significantly lower in the clodronate group than in the control group. Only 6 patients died in the clodronate group, whereas 22 died in the control group. The mean number of bony metastases per patient in the clodronate group was roughly half that in the control group. Thus, clodronate can reduce the incidence and number of new bony and visceral metastases in women with breast cancer who are at high risk for distant metastases.

ORAL CONTRACEPTIVES AND OVARIAN CANCER

Approximately 10% of cases of invasive epithelial ovarian cancer are hereditary, occurring predominantly in women with germ-line mutations in the BRCA1 or the BRCA2 gene. The lifetime risk of ovarian cancer is approximately 45% among women with BRCA1 mutations and 25% among those with BRCA2 mutations. Two current strategies for reducing the risk of ovarian cancer in women with these mutations include prophylactic oophorectomy and ultrasound screening, but the extent of risk-reduction associated with either of these procedures is not known. A third potential strategy is chemoprevention. Previous studies in 1991 and 1992 indicated that the risk of ovarian cancer was reduced about 50% in unselected women taking oral contraceptives for a long time.

To evaluate the potential benefits of oral contraceptive use in women at high risk for ovarian cancer, Narod and colleagues (12) for the Hereditary Ovarian Cancer Clinical Study Group studied 207 patients with BRCA1 (179 women) or BRCA2 (28 women) mutations and ovarian cancer, and 161 of their sisters who served as controls. Fifty percent of the patients and 70% of the control women reported a history of oral contraceptive use. The risk of ovarian cancer was decreased in the women taking oral contraceptives, and the degree of that decrease was roughly proportional to the duration of oral contraceptive use. Women who took an oral contraceptive agent for 6 or more years had a reduction in risk of 60%. The reduction in risk was similar for carriers of the BRCA1 and BRCA2 mutations. These data suggest that the administration of an oral contraceptive agent should be considered as part of a program of prevention for women with BRCA1 or BRCA2 mutations who have not had ovarian cancer. The magnitude of protection (approximately 50%) against hereditary ovarian cancer suggested by these results is considerably less than that possible
with prophylactic oophorectomy. Questions remain whether oral contraceptive use could increase the already high risk of breast cancer in women with BRCA1 or BRCA2 mutations.

**SHAKEN-BABY SYNDROME**

In 1972, Caffey described the “shaken-baby syndrome” as a combination of subdural and subarachnoid hemorrhage with traction metaphyseal fractures and retinal hemorrhages. Subsequently, there has been disagreement about which features comprise the syndrome and how shaking might cause them. Some infants injured or killed in this way also have clinical, radiologic, or necropsy evidence of blunt impact to the head, and other infants have no external signs of injury to the head. Thus, the definition of shaken-baby syndrome is uncertain, and some children with subdural hematomas due to other causes have been misdiagnosed as having shaken-baby syndrome, with parents or caregivers accused of assault. The 3 recent cases receiving great publicity with the deaths of babies Joseph Makin, Mathew Eappen, and Caroline Jongen have brought this syndrome to the forefront. A recent editorial in The Lancet cautioned that the increased awareness of this syndrome because of these 3 deaths and subsequent trials should be tempered with caution against overdiagnosis (13).

**CARDIAC HYPERPLASIA**

When I was in medical school, enlargement of the prostate gland was attributed on most occasions to “benign prostatic hypertrophy.” Today it appears that prostate gland cells can divide, and, therefore, hyperplasia is a normal and continuing occurrence in that gland as well as hypertrophy. In contrast to the prostate gland, hyperplasia of myocardial cells after a few months of life has been thought not to occur. The idea has been that a person attains an adult number of myocytes within a few months of birth and that these contract on average 70 times per minute throughout life. Myocytes consequently must be structurally and functionally immortal. A recent study by Kajstura and colleagues (14) from Valhalla, New York, calculated that the average heart of a 45-year-old man contains \( 5.8 \times 10^9 \) myocytes and that about 10% of these myocytes undergo mitosis each year. They calculated that mitosis lasts for \(< 1\) hour and that \(0.61 \times 10^9\) myocytes are formed in a healthy left ventricle each year. By light microscopy, it is common to see myocardial cells with 2 nuclei. I have never seen a mitotic figure in a myocardial cell of an adult human.

**TOP-SELLING PRESCRIPTION DRUGS IN 1997**

Listed in *Table 2* are the top-selling prescription drugs in 1997 as compiled by IMS-America and the Food and Drug Administration (15).
INTERNET PRESCRIBING

Travel agents, book vendors, and stockbrokers are already there. Internet consultations with physicians are already there. Even though some physicians oppose even telephone prescribing, Internet prescribing is beginning (16). In 1997, 2.5 billion prescriptions were dispensed in the USA. On-line selling, or “e-commerce,” is now estimated at $1.8 billion annually. Probably most physicians believe that Internet prescribing is appropriate only if a doctor-patient relationship already exists. Presently, most prescriptions from CyberDocs, an online virtual doctor’s office, have been for male hair loss and for emergency birth control (the “morning-after” pill). Internet prescribing, however, appears to be increasing. Interstate prescribing and the prescribing of narcotics or antidepressants via the Internet is, obviously, dangerous.

Y2K AND THE HEALTH CARE FINANCING ADMINISTRATION

The Heath Care Financing Administration was recently called on the carpet at a House hearing by the chairman of the Ways and Means health subcommittee because its basic systems are not yet millennium compliant (17). Only one third of its systems are now set for January 2000. Noncompliance, of course, would produce payment delays that would adversely impact the delivery of primary care services to Medicare beneficiaries. If Medicare is not 100% compliant by the year 2000 (coined as Y2K), it will probably make little difference that Baylor and other health care systems are millennium compliant at that time.

JIM MURRAY (1920 -- 1998)

Jim Murray, the Pulitzer Prize–winning sportswriter of nearly 40 years for the Los Angeles Times, died in August 1998 at age 78 at home shortly after writing a column for his paper’s Sunday edition (18). He was named “America’s Best Sportswriter” 14 times by the National Association of Sportscasters and Sportswriters. And it is not difficult to see why. On the death of basketball player Hank Gathers, for example, he wrote: “Death should stay away from young men’s games. Death belongs in musty hospital rooms, sickbeds. It should not impinge its terrible presence on the celebrations of youth, reap its frightful harvest in fields

<table>
<thead>
<tr>
<th>Drug</th>
<th>Classification</th>
<th>1997 sales (millions)</th>
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<tbody>
<tr>
<td>Prilosec</td>
<td>heartburn and acid reflux</td>
<td>$2300</td>
</tr>
<tr>
<td>Prozac</td>
<td>antidepressant</td>
<td>$1900</td>
</tr>
<tr>
<td>Zocor</td>
<td>cholesterol reducer</td>
<td>$1400</td>
</tr>
<tr>
<td>Epogen</td>
<td>red blood cell stimulator</td>
<td>$1200</td>
</tr>
<tr>
<td>Zoloft</td>
<td>antidepressant</td>
<td>$1200</td>
</tr>
<tr>
<td>Zantac</td>
<td>heartburn and acid reflux</td>
<td>$1100</td>
</tr>
<tr>
<td>Paxil</td>
<td>antidepressant</td>
<td>$946</td>
</tr>
<tr>
<td>Norvasc</td>
<td>calcium antagonist</td>
<td>$91f</td>
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<tr>
<td>Claritn</td>
<td>antihistamine</td>
<td>$90f</td>
</tr>
<tr>
<td>Vasotec</td>
<td>antihypertensive</td>
<td>$84f</td>
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where cheers ring and bands play and banners wave.”

On Ben Hogan, his hero, he wrote: “He was barely 5’7”, couldn’t have weighed 125. His butt was so nonexistent his hip pockets ran together. His clubs had a remnant-barrel look, and his clothes, while neat, had a mail-order look about them.”

WHAT MAKES THE USA SPECIAL?

Many newspapers in the USA on July 4th contained lists of things that Americans should be grateful for. The editorial staff of the Dallas Morning News provided a list in their lead editorial of that day of 201 things Americans should be grateful for. Although one was “laboratories where scientists and graduate students pursue knowledge and cures,” there was no mention of the medical system in the USA, which is the best in the world. If one has to get sick on Planet Earth, the place to be sick is in the USA. Only those who have sought medical care in non-US countries can fully appreciate the excellence of the medical system we have in this nation.

THE BEST HOSPITALS IN THE USA

Since 1990, U.S. News & World Report annually has ranked the best hospitals in the USA (19). Criteria used for rankings are reputation, which encompasses the reputation scores from an annual survey of 150 board-certified specialists in each of 16 specialties -- 2400 in all; mortality; and at least 1 of these 3 requirements: affiliation with a medical school, membership in the Council of Teaching Hospitals, or having a minimum of 9 of 17 key technologies readily available. Of the 6400 US hospitals, 1985 met the initial eligibility tests. The final rankings included 132 different hospitals. Of the 16 subspecialties analyzed (which included 42 hospitals in 12 specialties, 24 hospitals in 1 specialty, 21 hospitals in 1 specialty, and 17 hospitals in 2 specialties), Baylor University Medical Center was included in 8: cardiology and cardiac surgery, 33rd of 42; gastroenterology, 14th of 42; geriatrics, 34th of 42; gynecology, 41st of 42; pulmonary disease, 25th of 42; rheumatology, 33rd of 42; urology, 36th of 42; and rehabilitation, 15th of 21.

Seven other hospitals in Texas appeared on 1 or more of the 16 subspecialty lists: Methodist Hospital (Houston), 5 of 16; University of Texas M. D. Anderson Cancer Center (Houston), 5 of 16; Hermann Hospital (Houston), 3 of 16; Parkland Memorial Hospital (Dallas), 3 of 16; Texas Heart Institute-St. Luke’s Episcopal Hospital (Houston), 1 of 16; Texas Children’s Hospital (Houston), 1 of 16; and Texas Institute for Rehabilitation and Research (Houston), 1 of 16. Thus, Baylor University Medical Center (Dallas) appeared on more of the subspecialty lists (8 of 16) than any other hospital in Texas!

WERE CLINTON A PHYSICIAN

If physicians were as indifferent to law and truth as the occupant of our highest office, they would be prevented from practicing. No university president, school principal, or chief executive officer would be allowed to remain in office if that individual’s conduct was similar to that of our President. Talent, ability, intelligence, and charm are not substitutes for honesty and integrity. Indifference to law and truth in the nation’s highest office only
nurtures similar behavior elsewhere.

ANTHONY ROBERT LYONS (1964 – 1998)

The January 1998 issue of the BUMC Proceedings contained an article by Dr. Anthony R. Lyons from Nottingham, United Kingdom, titled “Total hip arthroplasty: osteolysis and its prevention with systemic therapy” (20). In the same issue, I interviewed Dr. Lyons (21) and was struck by the intelligence, talent, energy, and graciousness of this very open and warm 34-year-old man. I recently learned that Anthony Lyons died on July 26, 1998, tragically and unexpectedly. What a loss to his family, to his friends, to his orthopedic surgical colleagues, and to those of us fortunate enough to have spent a bit of time with this charming man.

William Clifford Roberts, MD
Editor in Chief

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