The Symbol of Modern Medicine

TO THE EDITOR: Drs. Wilcox and Whitham missed several important points of history in their article about serpentine symbols of medicine (1). Regarding the Asklepian, their article makes no mention of the healing staff of Moses: “And Moses made a serpent of brass, and put it upon a pole, and it came to pass, that if a serpent had bitten any man, when he beheld the serpent of brass, he lived” (2). The Book of Numbers dates from 1444 to 1405 BC (3), while the cult of Asklepios is said to date from the sixth century BC (4).

Wilcox and Whitham also missed the importance of the U.S. Public Health Service’s adoption of the caduceus in 1871, 31 years before the U.S. Army adopted it. The Public Health Service seal was originally developed by John Maynard Woodworth, the first supervising surgeon (the title was later changed to surgeon general) of the Marine Hospital Service (forerunner of the Public Health Service). It featured a caduceus crossed with a fouled anchor, the latter signifying sick or disabled seamen. The use of the caduceus to represent medicine was not so common in 1871, and it was more often associated with the god Mercury and used to symbolize trade or commerce. Woodworth used the caduceus of Mercury specifically because of the Public Health Service’s relationship with merchant seamen and the maritime industry (5).

The authors’ premise, that the caduceus is misused in the United States because of ignorance of ancient mythology, is incorrect. The Public Health Service chose the caduceus not while misunderstanding the mythology but as a purposeful representation of its history. As the Public Health Service evolved and grew to encompass a greater breadth of medicine, so too did the caduceus come to represent medicine. Symbols, like language, change with time. The caduceus and fouled anchor have been the proud symbol of the Public Health Service for 133 years.

Michael E. Toedt, MD
Dominique M. Gooby Toedt, MD
Jackson General Hospital, Millcreek Family Medicine
Ripley, WV 25271

References

TO THE EDITOR: I enjoyed the erudite article by Drs. Wilcox and Whitham about the symbol of medicine (1). Semiotics is defined as “a general philosophical theory of signs and symbols that deals especially with their function in both artificially constructed and natural languages, and comprises the three branches of syntaxics, semantics, and pragmatics.” Semiotics was first studied by Swiss linguist Ferdinand de Saussure in the early 20th century and was later advanced by Roland Barthes (1915–1980) of France.

Carl G. Jung wrote, “A symbol is a term, a name, or even a picture that may be familiar in daily life, yet that possesses specific connotations in addition to its conventional meaning” (2). Symbols can often be interpreted in more than one way and can stir native passion.

During the past 2 decades, medicine in the United States has turned into a free-market business enterprise that would flatter the legacy of Hermes. If the wrong symbol—the caduceus—is entrenched in the medical culture, the learned profession must revise this error. Ignorance and hubris explain this “phenomenon” in a climate of revisionism.

In Occidental perception, the snake represents evil. The serpent on the staff represents the healing arts. We may not be able to correct the parallax in perception as long as the neo-Paganism of bottom-line worship dominates the ethos of the health care industry. Some doctors (like Michael Swango) have acted as snakes in white coats.

Neni Prasad, MD
Springfield, IL 62704

The Symbol of Modern Medicine

TO THE EDITOR: I enjoyed the recent article by Drs. Wilcox and Whitham (1) discussing the solo serpent of the Asklepian as the appropriate symbol of modern medicine rather than the entwined double serpents of the caduceus. While I agree that the Asklepian is more authentic historically and mythologically, the caduceus has important meaning for modern medicine, too.

In college, I enjoyed the novel The Canning Man by Robertson Davies (2). The protagonist is an old, wise Canadian physician who throughout his career tries to balance competing forces in medicine. He adorns his office with a specially made caduceus depicting 2 Canadian rattlesnakes entwining Mercury’s staff. When asked about it, he answers that “...I shall have on my wall a constant reminder of the Warring Serpents of Hermes—Knowledge and Wisdom, balanced in an eternal tension.” The dialogue continues:

Knowledge being science and all the accumulated lore you have pumped into you at medical school; science which keeps changing and shifting all through your lifetime, like a snake shedding its old skin—

And Wisdom, with which you have to apply and temper the whole business, and fit it to the patient who sits before you, so that it too has a serpentine sinuosity and of course the wisdom which snakes are—quite mistakenly—supposed to possess (2).

The analogy extends to many elements of modern medical practice: the art of medicine versus the science of medicine, subjective data versus objective data as embodied in the classic SOAP (Subjective, Objective, Assessment, Plan) format, the balance between aggressive treatment and palliative care in the dying, the body’s natural homeostatic mechanisms, even the modern tension between professional ideals and the business of medicine. The caduceus, although not the
original symbol of the profession, reminds us that everything requires careful balance.

The authors provided an intriguing discussion of the ancient origin of both symbols. I was reminded of my undergraduate parasitology course and the text *Foundations of Parasitology* (3), which suggested that the practice of treating dracunculiasis by winding worms out of the skin on a stick may have been the original inspiration for both the Asklepiean and the caduceus. Did this ancient practice find its way into the symbolism for the myths of Asklepios and Hermes?

Finally, I did not know until reading this article that the 2-serpented caduceus has been associated with the medical profession only since its 1902 adoption by the U.S. Army Medical Corps. Unlike our Army colleagues, we in the U.S. Air Force Medical Corps use the Asklepiean on our badge. An image of the insignia can be viewed at www.af.mil/photos/images/art_badges_0026.jpg, and the seal of the U.S. Air Force Medical Service can be seen at www.af.mil/search/media.asp?mediaID=5813&mediaType=2.

Adrian G. Letza, MD, Captain
U.S. Air Force Medical Corps
Wilford Hall Medical Center
San Antonio, TX 78236

Disclaimer: The views expressed in this letter are the author’s and do not represent the views of the U.S. government.

References

TO THE EDITOR: Drs. Wilcox and Whitham (1) trace the origin of the healing imagery of a snake on a staff to the Greek tradition of Asklepios. However, an earlier reference to Moses in the Hebrew Bible describes the healing power of this symbol centuries before the Greeks: "Hashem said to Moses, 'Make yourself a burning one and place it on a pole, and it will be that anyone who has been bitten will look at it and live.’ Moses made a snake of copper and placed it on the pole; so it was that if the snake bit a man, he would stare at the copper snake and live'” (2). In agreement with the authors’ position, the Bible refers to only one snake. Clearly, the Hebrew Bible was well known to the Greeks, since it was translated into Greek from the Hebrew and is known as the Septuagint.

Meyer D. Lifschitz, MD
Veterans Affairs Hospital and University of Texas Health Science Center at San Antonio
San Antonio, TX 78229-4404

References

TO THE EDITOR: Drs. Wilcox and Whitham (1) might like to know an alternative explanation as to why the Asklepiean evolved as the symbol of our profession. While I was studying parasitology as an undergraduate, my professor referenced treatment for guinea worm disease, otherwise known as dracunculiasis, as the source for the single serpent entwined around a staff. The adult female *Dracunculus medinensis* can reach 2 to 3 feet in length. Approximately 10 to 14 months after an infection, larvae are released within the intestine and the adults enter the skin and cause painful papules, usually on the lower extremities but also on the upper extremities, trunk, genitalia, or buttocks. As the mature female attempts to exit the skin, a painful blister may form and the worm then begins to emerge from the skin. Because of the length of the worm and its rather tight burrow within the epidermis, it cannot be pulled out at once. Rather, the worm is typically wound around a stick; practitioners apply gentle traction and loop the worm around the stick several centimeters at a time. It can take weeks until the entire worm is extracted. Thus, my professor contended that the appearance of a guinea worm wound around a stick may have been the precursor of the Asklepiean. My professor was also bemused about the origins of the dual-serpent caduceus replete with wings, that is, the symbol of Mercury. He saw the caduceus as the symbol of commerce and the symbol of commerce and finance, and rather than believing it was erroneously used as the U.S. symbol of medicine, he thought it was a careful choice by those members of the medical profession who were more interested in lucre than in patient care.

As a former naval medical officer, I would never cast aspersion on the symbol of the U.S. Army Medical Corps. Perhaps Drs. Wil-
TO THE EDITOR: After reading the interesting review of the chronic confusion in the United States between the caduceus and Askleopian symbols (1), I wondered whether the twin-serpent emblem of Hermes—god of commerce and wealth, patron of merchants and thieves, and escort of the dying to the underworld—might be the more appropriate symbol for U.S. medicine at present. Asklepios was a “focus of . . . supplication . . . for the poor and disregarded” (1). While the poor continue to be disregarded and have little access to physicians outside of last-resort settings such as chaotic emergency departments, merchant medicine is thriving. Medical practice has always been to some extent a commercial enterprise, but in recent decades we Americans have appeared increasingly conflicted about whether medicine is at heart a humanistic healing art or simply a commodity that should be traded in the open marketplace (2). As long as business administrators without medical training and solely concerned with the bottom line continue to make health care decisions with impunity, the unethical Hermes and his caduceus will remain in the ascendancy. In addition, while the snake of the Asklepiian is ascending the staff and escaping the underworld, the inroads made by physician-assisted suicide in recent years demonstrate that the efficient passage to the River Styx promised by Hermes is increasingly becoming the prerogative of physicians.

Also, the review does not mention that the serpent on a staff as a healing emblem predates Asklepios. For instance, the Book of Numbers relates an episode that occurred when the Israelite tribes wandering in the wilderness were afflicted by vipers: “And Moses made a serpent of brass, and put it upon a pole, and it came to pass, that if a serpent had bitten any man, when he beheld the serpent of brass, he lived” (3).

David P. Steensma, MD
Mayo Clinic
Rochester, MN 55905

References

TO THE EDITOR: I read with interest the article by Wilcox and Whitham (1) about the symbol of medicine. The double serpent and wings, the caduceus, which is often used as the insignia of many medical organizations, in fact has no medical relevance. The Latin word caduceus is an alteration of the Greek word karykeion, from karyx, meaning a “herald’s wand.” According to Greek mythology, the caduceus was the magical rod of Hermes, who was the god of commerce, invention, cunning, and theft and who also served as messenger, scribe, and herald for the other gods (2). During the Middle Ages, the caduceus appeared on printers’ signs and merchant ships, symbolizing their role as messengers and businessmen. Of interest, it has been placed on the front of commercial buildings such as banks, symbolizing Hermes as the patron of trade (3).

The staff of Asklepios entwined by a single serpent is the true symbol of medicine and has a historical connection with the practice of medicine. In Greek sculpture, Asklepios was represented standing, dressed in a long cloak, with bare breast; his usual attribute was a staff with a single serpent coiled around it. The serpent in ancient times represented wisdom, health, and immortality. It was considered to be the most powerful symbol against disease because the serpent renews itself every year as it gets a new skin and sheds its old one. This ability has been associated with the circle of life and the spirit of renaissance that has been present since early Hellenic antiquity.

I suggest the Greek word iatros for the staff of Asklepios because it perfectly denotes the correct meaning for the emblem of the medical profession. Iatros means physician and sema means sign or symbol. From iatros derive such words as iatrogenic, and from sema derive such words as semantic (4).

Konstantinos Paparounas, MD, PhD
Hatzikosta General Hospital of Ioannina
Ioannina 45001, Greece

References

TO THE EDITOR: I read with interest the article by Wilcox and Whitham (1) on the symbol of modern medicine. The question of one snake or two is interesting from a historical standpoint. However, the more important question is which should be the symbol of modern medicine. The answer is simple, after the 50th anniversary of Watson and Crick’s great discovery (2): The symbol should be 2 snakes intertwined in a double helix.

Jamie Newmann, MD
Mayo Clinic College of Medicine
Rochester, MN 55902

References

IN RESPONSE: We are delighted that our article generated so much interest, and we are happy to address questions raised in correspondence. In-depth coverage will appear in our forthcoming book. Given the necessary brevity of our article, we were unable to include every theory behind the serpent and staff motif. Regarding the guinea worm theory proposed by Müller (1), this attractive piece of post hoc speculation has developed substantial
popular appeal within the medical community but has no standing in the light of extensive historical and archaeological evidence. The Asklepian has its origins in the strong association between serpent worship and healing cults throughout the pre-Hellenic Mediterranean, North African, and Eastern cultures (2–4). In artistic portrayals from the Egyptian old kingdom (2800 to 2250 BC), the goddesses Nekhebet and Sat ti are commonly depicted presenting Horus with the gifts of life and sovereignty, symbolized by a staff encircled by a single serpent (2). The serpent motif has long been associated with the gift of life and renewal in many cultures, but only in the cult of Asklepios was this association so purely medical (2–4).

Several correspondents noted the resemblance of the Asklepian to the biblical “serpent of brass,” which Moses used to miraculously cure snake bites (5). Indeed, plaque medals that depicted Moses holding the brass serpent became popular religious icons during the 14th century. They were worn in the hope of evoking the protection of Jesus and God against the bubonic plague, just as the Greeks and Romans of antiquity had used charms to evoke the protection of Asklepios (6). The brass serpent of Moses was a very popular Renaissance motif and was prominently depicted by Michelangelo in the Sistine Chapel. Schouten wrote, “In my opinion, this emblem, the brass serpent, greatly influenced the 16th century renaissance of the classical Aesculapius and his attribute, the rod and serpent, when Humanism infused new life into a number of antique motifs” (6). This symbol is known as the Tau cross and is featured on the coat of arms of the Royal Society of Medicine of the United Kingdom, where it is often mistaken for an Asklepian.

A caduceus symbol was actually first used by the U.S. Army between 1851 and 1887 to indicate the noncombatant status of hospital stewards; it was later replaced by the Red Cross (4). The U.S. Marine Hospital Service (the forerunner of the U.S. Public Health Service) then adopted a seal consisting of a caduceus and fouled anchor (4, 7, 8). However, the official history of the Public Health Service states that “the caduceus of mercury appears in the corps device because of its relationship with merchant seamen and the maritime industry” (7). Thus, the adoption of the caduceus symbol by the Public Health Service had no direct medical connotation but was used to symbolize seamen and the maritime trade, as was popular throughout the 18th and 19th centuries (3). Of interest, just like the U.S. Army Medical Corps, the Public Health Service seal inappropriately displays a modern caduceus (resembling that of the publisher Churchill) and not the ancient caduceus of Hermes–Mercury.

We liked Dr. Paparounas’s suggestion but would prefer the combined term Asklepianiatrosena. However, we believe that Dr. Newman’s suggested introduction of a third serpentine symbol consisting 2 snakes in a right-handed helix mimicking DNA would be entirely counterproductive. After all, the DNA of mice, rats, and monkeys is in essence very similar to that of humans, and we therefore champion the Asklepin symbol because it reminds us of the essentially humanistic nature of medical practice. An inscription found at the Asklepieion of Athens speciﬁes the Asklepian commitment: “These are the duties of a physician . . . he would be like the God, savior equally of slaves, of paupers, of rich men, of princes and to all a brother such help he would give” (9). The Asklepine tradition emphasizes integrity, sacriﬁce, compassion, and universal access to health care. People are most equal in their capacity for illness and suffering. Thus, physicians must seek to practice their craft without primary regard for the social status of their patients, personal advancement, or ﬁnancial rewards. As Sir William Osler wrote, “The practice of medicine is an art, not a trade; a calling, not a business; a calling in which your heart will be exercised equally with your head” (10).

Robert A. Wilcox, BMBS, BSc(Hons), PhD
Emma M. Whitham, MBBS, BSc(Hons), PhD
Flinders Medical Centre
Bedford Park, South Australia 5042, Australia

References

High-Dose and Low-Dose Cosyntropin Stimulation Tests for Diagnosis of Adrenal Insufﬁciency

TO THE EDITOR: Dorin and colleagues (1) compared the 250-µg and 1-µg cosyntropin stimulation tests for diagnosis of secondary adrenal insufﬁciency. Using complex statistical methods, they concluded that both tests perform similarly. The authors reported that they searched the MEDLINE database for all relevant English-language papers published between 1966 and 2002. They found 9 papers comparing the 1-µg test with insulin tolerance or metyrapone tests and 7 papers also comparing it with the 250-µg test. Unfortunately, they failed to find on MEDLINE 3 additional studies pointing to an advantage with the 1-µg test.

Rose and colleagues (2), in a study of 158 patients, found that the 250-µg test misses most diagnoses of adrenocorticotropic hormone deﬁciency, with a sensitivity of 21%, a speciﬁcity of 100%, and 68% accuracy. In contrast, the 1-µg test had 100% sensitivity, 68% speciﬁcity, and 90% accuracy. Gandhi and associates (3) found that 9 patients showed adrenal insufﬁciency with the 1-µg test but had a normal response to the 250-µg test. Seven of these patients had insulin tolerance testing, and in 6, adrenal insufﬁciency was conﬁrmed. In another 16 patients, results of both cosyntropin stimulation tests were abnormal. Choi and coworkers (4) examined 72 patients using insulin tolerance tests for comparison and found that the 1-µg test had a sensitivity of 97%, a speciﬁcity of 78%, a positive predictive value of 81%, and a negative predictive value of 97% for secondary adrenocortical insufﬁciency.
The authors stated, "The sensitivity of the [1-μg test] was 100% . . . with no falsely reassuring results. [The 250-μg test] . . . was less sensitive . . . it produced 2 of 64 (3%) falsely reassuring results."

Furthermore, Dorin and colleagues did not correctly cite findings in 2 of the papers they described. They reported that in Abdu and colleagues’ work (5), the specificity of both the 1-μg and 250-μg tests was 100%. However, in the abstract of Abdu and colleagues’ paper, the authors stated, "The sensitivity of the [1-μg test] was 100% . . . with no falsely reassuring results. [The 250-μg test] . . . was less sensitive . . . it produced 2 of 64 (3%) falsely reassuring results."

Dorin and colleagues also claimed that in Mayenknecht and colleagues’ paper (6), sensitivity was equal for both cosyntropin stimulation tests. However, in Figure 2 in that paper, among the 14 patients with clear pathologic results on the insulin tolerance test, at least 1 and probably another patient (with a cortisol level of about 700 nmol/L at 60 minutes!) had false-negative results on the 250-μg test and true-positive results on the 1-μg test.

Dorin and colleagues’ method of comparing all high-dose with low-dose tests and calculating cutoff points by areas under the curve is problematic for 2 reasons. First, studies of the 250-μg test start in 1976 and those of the 1-μg test start in 1996. This makes it difficult to compare methods used. Second, results of cosyntropin stimulation tests differ substantially in absolute values according to the methods used (7). Cutoff points should therefore be calculated for each laboratory on the basis of each laboratory’s own normal results. Only studies performed by the same laboratory, mainly for the same patients, should be used to compare the performance of different tests.

The Figure shows sensitivity and specificity according to this guideline. Calculation of total accuracy for the 9 studies was 90.1% for the 1-μg test and 83.9% for the 250-μg test. This, together with the results in the Figure, shows a clear advantage of the 1-μg test over the 250-μg test.

Gabriel Dickstein, MD
Bnai Zion Medical Center
Haifa 31048, Israel

References

IN RESPONSE: The paper by Gandhi and associates (1) was excluded from our analysis because of inadequate stratification of patients by gold standard testing (only 7 of 31 patients had an insulin tolerance or metyrapone test). The paper by Choi and coworkers (2) appeared on MEDLINE in April 2003, after our final draft was submitted, and includes 72 patients who underwent the 1-μg test and the insulin tolerance test. The paper by Rose and colleagues (3) was not detected by our MEDLINE search and includes 2 separate samples of pediatric patients: 38 who had 250-μg testing and metyrapone testing and 120 who at a later time had the 1-μg test and metyrapone testing. Thus, none of these 3 studies are useful for head-to-head testing of the 250-μg and 1-μg tests. When the data of Choi and coworkers (2) and Rose and colleagues (3) are included in our Tables 2 and 4 and subjected to a summary receiver-operating characteristic (ROC) analysis, there is no change in our conclusion that the operating characteristics of the 250-μg and 1-μg tests are virtually identical (no difference in area under the curve, the value of sensitivity, or specificity at a specificity of 95%; P > 0.2 for all comparisons).

In the paper by Abdu and colleagues (4), the data in their Table 1 for all 42 patients who had an insulin tolerance test as the gold standard revealed that the sensitivity was 100% for both cosyntropin stimulation tests at cutoff cortisol levels of 500 nmol/L and 600 nmol/L. In the paper by Mayenknecht and colleagues (5), an analysis of paired ROC data in our Appendix Figure firmly establishes that the performance characteristics of the 250-μg and 1-μg tests are indistinguishable.

Averaging sensitivities and specificities to perform a t-test is inappropriate for meta-analysis. For this method to be valid, specificities would have to be equalized, which is not possible with the available data. Summary ROC methods were designed to deal with these difficulties and facilitate comparison between studies because they assess performance characteristics independent of cut-score. Dr. Dickstein’s Figure shows inequality of specificities, and the data are underpowered to conclude that specificities are not different (P =
0.092). Calendar time is less of an issue, since both the 250-μg and the 1-μg tests were compared with stable gold standard tests. To address the issue of direct comparisons, we analyzed the 7 studies that met our inclusion criteria and compared the 1-μg and the 250-μg tests head-to-head in the same sample of patients (Tables 2 and 4); we found no difference between the tests for any parameter of test performance (area under the curve, value of sensitivity, or sensitivity at a specificity of 95%; P > 0.2 for all comparisons).

Perhaps the 1-μg test has marginally superior performance characteristics in carefully selected samples, but our inclusive analysis using appropriate methods demonstrates no difference in test performance or sensitivity when specificity is equalized. The apparent increase in sensitivity associated with the 1-μg test derives from selection of a high cortisol cut-score, which shifts up along the ROC curve and improves sensitivity at the expense of lower specificity. For a disorder such as secondary adrenal insufficiency, where pretest probability is typically 10% to 30%, the utility of a diagnostic test with low specificity is limited because of the large number of false-positive results. As a numerical example, a cut-score that achieves 95% sensitivity for the 1-μg test in our Figure 1 matches a specificity of 60% and yields a positive likelihood ratio of only 2.4. At a 30% prevalence of adrenal insufficiency in 100 patients tested, there would be 28 false-positive test results and an equal number of true-positive test results. All 56 patients with positive results on the 1-μg test would then require additional sorting by gold standard tests to address the issue of direct comparisons, we analyzed the 7 studies that met our inclusion criteria and compared the 1-μg and the 250-μg tests head-to-head in the same sample of patients (Tables 2 and 4); we found no difference between the tests for any parameter of test performance (area under the curve, value of sensitivity, or sensitivity at a specificity of 95%; P > 0.2 for all comparisons).

Perhaps the 1-μg test has marginally superior performance characteristics in carefully selected samples, but our inclusive analysis using appropriate methods demonstrates no difference in test performance or sensitivity when specificity is equalized. The apparent increase in sensitivity associated with the 1-μg test derives from selection of a high cortisol cut-score, which shifts up along the ROC curve and improves sensitivity at the expense of lower specificity. For a disorder such as secondary adrenal insufficiency, where pretest probability is typically 10% to 30%, the utility of a diagnostic test with low specificity is limited because of the large number of false-positive results. As a numerical example, a cut-score that achieves 95% sensitivity for the 1-μg test in our Figure 1 matches a specificity of 60% and yields a positive likelihood ratio of only 2.4. At a 30% prevalence of adrenal insufficiency in 100 patients tested, there would be 28 false-positive test results and an equal number of true-positive test results. All 56 patients with positive results on the 1-μg test would then require additional sorting by gold standard tests to distinguish true- and false-positive results. Alternatively, normal patients without abnormal hypothalamic–pituitary–adrenal function would be unnecessarily managed with lifelong corticosteroid replacement. On the other hand, a specificity of 95% matches a sensitivity of 61% for the 1-μg test; at a prevalence of 30% in 100 tested patients, there would be 3.5 false-positive test results and an equal number of true-positive test results. All 56 patients with positive results on the 1-μg test would then require additional sorting by gold standard tests to distinguish true- and false-positive results. Alternatively, normal patients without abnormal hypothalamic–pituitary–adrenal function would be unnecessarily managed with lifelong corticosteroid replacement. On the other hand, a specificity of 95% matches a sensitivity of 61% for the 1-μg test; at a prevalence of 30% in 100 tested patients, there would be 3.5 false-positive test results and an equal number of true-positive test results. At a clinically practical level of specificity (for example, 95%), neither the 250-μg test nor the 1-μg test achieve a sufficient level of sensitivity to obviate the need for integrated tests of hypothalamic–pituitary–adrenal function when the results of the corticotropin stimulation test are negative and clinical suspicion for adrenal insufficiency based on pretest probability is substantial. In the event that a test with high sensitivity but low specificity finds a role in the screening algorithm for adrenal insufficiency, our results, which show equivalency of the 1-μg and 250-μg tests, indicate that the algorithm could be made more practical simply by raising the cortisol cut-score for the 250-μg test.

Richard I. Dorin, MD
Clifford R. Qualls, PhD
New Mexico Veterans Affairs Healthcare System and University of New Mexico School of Medicine
Albuquerque, NM 87108

Lawrence M. Crape, MD, PhD
Santa Clara Valley Medical Center
San Jose, CA 95128

References

CLINICAL OBSERVATIONS

Responsiveness of Thrombotic Thrombocytopenic Purpura to Rituximab and Cyclophosphamide

TO THE EDITOR: We agree with Zheng and colleagues (1) that rituximab is a promising alternative to all other immunosuppressive treatments in chronic relapsing thrombotic thrombocytopenic purpura due to an acquired deficiency in von Willebrand factor–cleaving protease (vWF-cp), ADAMTS13. However, data regarding the use of rituximab as a single agent in thrombotic thrombocytopenic purpura are particularly scarce. We report our experience with rituximab as monotherapy in a patient with relapsing thrombotic thrombocytopenic purpura due to an anti–ADAMTS13 antibody.

A 38-year-old man had a 24-year history of relapsing thrombotic thrombocytopenic purpura. Between 1978 and 2001, he had 13 relapses requiring protracted infusions of fresh frozen plasma, plasma exchanges, or both. He received several treatments between 1973 and 2000, including high-dose steroids, intravenous immunoglobulins, and vincristine. Despite a splenectomy in 1997, 4 severe relapses occurred. Activity of vWF-cp was repeatedly undetectable (<5%; normal range, 50% to 100%) over 3 years, and anti-protease antibody remained detectable during relapses as well as between them (Figure). In 2002, the patient was admitted for a relapse of thrombotic thrombocytopenic purpura with neurologic disturbances requiring mechanical ventilation. Protracted plasma exchanges and fresh frozen plasma infusions led to remission. After giving informed consent, the patient received 4 infusions of rituximab (MabThera, Roche, Basel, Switzerland) per week (375 mg/m²). He had not received any other immunosuppressive treatment in the past 3 years. After the second rituximab infusion, fresh frozen plasma infusion was discontinued. At 74 days of therapy, vWF-cp activity reached 24% and anti-protease antibody was faintly detected. A fifth infusion of rituximab was performed as maintenance therapy at day 96. At 168 days of therapy, vWF-cp activity increased to 43% and anti-ADAMTS13 antibody was undetectable. Seven months after plasma therapy was discontinued, the patient was doing well and thrombotic thrombocytopenic purpura had not recurred.

Our preliminary data indicate that rituximab alone may prove to be an optimal immunosuppressive therapy for chronic–relapsing thrombotic thrombocytopenic purpura due to anti–vWF-cp antibodies.
Figure. Evolution of time of plasma von Willebrand factor–cleaving protease (vWF-cp) activity before and after treatment with rituximab.

Plasma vWF-cp activity was measured during 3 relapses (R) before (*) and after (†) plasma exchange or after fresh frozen plasma infusions (‡) and during remission (§). The evolution over time of CD19⁺ cell count and total serum immunoglobulin level is also indicated. + = high titer; +/- = low titer; vWF = von Willebrand factor.

Fadi Fakhouri, MD
Luis Teixeira, MD
Richard Delarue, MD
Jean-Pierre Grünfeld, MD
Hôpital Necker
75015 Paris, France

Agnès Veyradier, MD, PhD
Hôpital Antoine-Béclère
92140 Clamart, France

Reference

CORRECTIONS

Correction: Diagnosis of Adrenal Insufficiency

In an article on diagnosis of adrenal insufficiency (1), Figure 2 contained an error. The box that reads “Suspicion of mild or recent-onset chronic renal insufficiency” should read “Suspicion of mild or recent-onset chronic adrenal insufficiency.”

Reference

Correction: Gatifloxacin-Induced Hepatotoxicity and Acute Pancreatitis

In a recent case report on gatifloxacin-induced hepatotoxicity and acute pancreatitis (1), one of the authors’ affiliations was listed incorrectly. A. Obaid Shakil, MD, is affiliated with the University of Pittsburgh, not Indiana Hospital.

Reference
Duration of Antibiotic Therapy for Lyme Disease

TO THE EDITOR: In his editorial on the duration of antibiotic therapy for Lyme disease, Allen Steere discussed the pathogenesis of chronic Lyme disease symptoms (1). Steere attributed these symptoms to a “postinfectious” autoimmune syndrome that is triggered by *Borreia burgdorferi* infection and cited human leukocyte function-associated antigen-1 (also known as human leukocyte function antigen type 1, or LFA-1) as a possible target autoantigen in chronic Lyme arthritis. This view is puzzling and surprising, because recent studies by Steere himself (2) and others (3) have discounted LFA-1 as a “relevant” autoantigen in chronic Lyme disease. Consequently, the role of autoimmunity in patients with persistent Lyme disease symptoms remains unsubstantiated.

At the same time, Steere dismissed the possibility of persistent spirochetal infection in chronic Lyme disease on the basis of a single long-term antibiotic trial in patients in whom previous Lyme disease therapy had failed (1). This trial had significant flaws in its design and execution, not the least of which was the absence of a valid long-term antibiotic regimen (4). In contrast, numerous animal and human studies point to the persistence of spirochetal infection and the need for rational long-term antibiotic treatment in patients with chronic Lyme disease (5). Recent molecular and immunologic findings support the presence of persistent infection and underscore the barriers to antibiotic efficacy in this protean illness (4, 5).

Steere cited the “evidence-based treatment recommendations” of the Infectious Diseases Society of America (IDSA) in deciding on treatment for patients with persistent Lyme disease symptoms. Unfortunately, the evidence invoked by the IDSA is inconclusive at best, and its guidelines have been used to justify patient neglect in chronic Lyme disease (6). Instead of following the compromised recommendations of the IDSA, we need to examine the clinical experience of patients with Lyme disease and their physicians in deciding how to treat persistent infection in chronic Lyme disease (4–6).

Raphael B. Stricker, MD
California Pacific Medical Center
San Francisco, CA 94108

Edward L. McNeil, MD
Bowen Microbiology Research Institute
Palm Harbor, FL 34684

References

IN RESPONSE: Drs. Stricker and McNeil quote my editorial incorrectly. It is important to distinguish chronic Lyme arthritis, in which a knee remains inflamed for months or several years despite antibiotic therapy, from chronic post–Lyme disease syndrome or so-called chronic Lyme disease, in which patients develop musculoskeletal, neurocognitive, or fatigue symptoms (similar to chronic fatigue syndrome or fibromyalgia) during or soon after Lyme disease despite standard antibiotic treatment for *Borreia burgdorferi* infection.

We have postulated that genetically susceptible patients with *B. burgdorferi*-infected knees may develop autoimmunity within the proinflammatory milieu of the joint because of molecular mimicry between an immunodominant epitope of outer-surface protein A and a host protein (1). A candidate molecular mimic was a sequence on the light chain of human lymphocyte function-associated antigen-1 (LFA-1 α1,32-340), but we have come to think that this is not a relevant autoantigen in this disease (2). We have never postulated that autoimmunity or LFA-1 has any role in the pathogenesis of chronic post–Lyme disease syndrome.

In contrast with the statement of Drs. Stricker and McNeil, the weight of evidence is against the idea that chronic post–Lyme disease syndrome or “chronic Lyme disease” results from active infection with *B. burgdorferi*. Although the spirochete has been seen in intraacellular locations in several tissue culture experiments, the organism has been seen only extracellularly in affected tissues from patients with Lyme disease (3). In a mouse model of Lyme disease, a few attenuated, noninfectious spirochetes were found in ticks that fed on the mice 3 months after 1-month courses of antibiotic therapy, but no mice had positive results 6 months after treatment (4).

Most important, long-term persistence of the spirochete has not been substantiated in any large series of patients treated with currently recommended antibiotic regimens. In a double-blind, placebo-controlled trial that sought to determine whether patients with persistent symptoms after Lyme disease would benefit from additional 3-month courses of antibiotic therapy (5), no patient had positive cultures or positive results by polymerase chain reaction before treatment, and no differences were noted in outcome between the antibiotic and placebo groups.

As with chronic fatigue syndrome or fibromyalgia, symptomatic treatment may be helpful for some patients with “chronic Lyme disease.” In addition, a team approach by health care professionals or cognitive behavioral therapy has been shown to be of value for some patients with chronic fatigue syndrome or fibromyalgia. There is no substitute for sympathetic listening and explanation.

Allen C. Steere, MD
Massachusetts General Hospital and Harvard Medical School
Boston, MA 02114

References
2. Steere AC, Falk B, Drouin EE, Baxter-Lowe LA, Hammer J, Nepom GT. Binding of outer surface protein A and human lymphocyte function-associated antigen 1 pep-

**Dark Rounds**

**TO THE EDITOR:** I read with sympathetic interest Dr. Fitzgerald’s essay about finding satisfaction in coming to work in the very early morning hours (1). She described the changed role of academic-based physicians over the past 20 years, a change not necessarily for the better in my opinion.

Academic-based physicians are functionally in private practice, and the emphasis on the daily coding of visits plus the billing for those visits is as acute in academia as anywhere. Teaching institutions expect their medical faculty to earn their keep by generating money for the institution. For most physicians in academic medicine, a periodic profit-and-loss statement is generated showing what an individual has cost the institution and what money he or she has brought in.

That Dr. Fitzgerald had to see almost a dozen new admissions to her medical team’s service in the preceding 24 hours represents the increased volume of patients the internal medicine services are receiving these days, and that is not good. One of the reasons that internal medicine is in decline is directly related to this common occurrence of a dozen admissions in a day with no time left for the intern, resident, or medical students to study those patients in detail. Internal medicine is all too often a cattle drive in humanity, and I believe that we are turning off more good future internists and subspecialists because of this. Who would want to be in internal medicine given that early experience? There are other fulfilling areas available, and younger physicians are voting with their feet.

The emphasis on teaching suffers. Faculty are not as available; services are fragmented and far-flung; and direct dialogue among attending physicians, consulting physicians, and housestaff is very difficult. For many faculty physicians, productivity has replaced teaching, and for physicians in training, too many admissions stifle enthusiasm and learning.

I see Dr. Fitzgerald’s coming to work in the very early morning hours as being her partial solution to the problem. It works for her, but it is an unusual lifestyle and, as she stated, not one that all could or should emulate. For all the reasons she described and more, internal medicine is a house badly in need of major repair.

*David Mullins, MD*

*Athens, GA 30606*

**Reference**