

## NITRO-BID® Plateau CAPS® (nitroglycerin) 2.5 mg, 6.5 mg, and 9 mg

### DESCRIPTION: Each NITRO-BID®

Controlled-Release Capsule contains:

2.5 mg nitroglycerin: Light purple and clear capsule with white beads; identification imprint MARION/1550.

6.5 mg nitroglycerin: Dark blue and yellow capsule with white beads; identification imprint MARION/1551.

9 mg nitroglycerin: Green and yellow capsule with white beads; identification imprint MARION/1553.

**ACTION:** The mechanism of action of nitroglycerin in the relief of angina pectoris is not as yet known. However, its main pharmacologic action is to relax smooth muscle, principally in the smaller blood vessels, thus dilating arterioles and capillaries, especially in the coronary circulation. In therapeutic doses, nitroglycerin is thought to increase the blood supply to the myocardium which may, in turn, relieve myocardial ischemia, the possible functional basis for the pain of angina pectoris. The sublingual administration of nitroglycerin is normally rapid and transient, but nitroglycerin in controlled-release NITRO-BID® 2.5, NITRO-BID® 6.5, and NITRO-BID® 9 produces a prolonged action.

**INDICATIONS:** Based on a review of this drug and a related drug by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications as follows:

“Possibly” effective:

For the management, prophylaxis, or treatment of anginal attacks.

Final classification of the less-than-effective indications requires further investigation.

**CONTRAINDICATIONS:** Acute or recent myocardial infarction, severe anemia, closed-angle glaucoma, postural hypotension, increased intracranial pressure, and idiosyncrasy to the drug.

**WARNINGS:** Capsules must be swallowed. FOR ORAL, NOT SUBLINGUAL, USE. NITRO-BID® 2.5, NITRO-BID® 6.5, and NITRO-BID® 9 Controlled-Release Capsules are not intended for immediate relief of anginal attacks.

**PRECAUTIONS:** Intraocular pressure may be increased; therefore, caution is required in administering to patients with glaucoma. Tolerance to this drug and cross-tolerance to other organic nitrites and nitrates may occur. If blurring of vision, dryness of mouth, or lack of benefit occurs, the drug should be discontinued.

**ADVERSE REACTIONS:** Severe and persistent headaches, cutaneous flushing, dizziness, and weakness. Occasionally, drug rash or exfoliative dermatitis and nausea and vomiting may occur; these responses may disappear with a decrease in dosage. Adverse effects are enhanced by ingestion of alcohol, which appears to increase absorption from the gastrointestinal tract.

**DOSAGE AND ADMINISTRATION:** Administer the smallest effective dose two or three times daily at 8- to 12-hour intervals, unless clinical response suggests a different regimen. Patient should be titrated to anginal relief or hemodynamic response. Hemodynamic response can be measured by drop in systolic blood pressure. Discontinue if not effective.

**HOW SUPPLIED:** NITRO-BID® (nitroglycerin) 2.5, 6.5, and 9 Controlled-Release Capsules are available in 60- and 100-count bottles.

**CAUTION:** Federal law prohibits dispensing without prescription.

**STORAGE:** Store at a controlled room temperature. Dispense only in the original unopened container.

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Another patient benefit product from



## Editor's Correspondence

*Contributions to this section may include comments on articles published in the ARCHIVES, or reports of unique educational character. Communications will be published as space and editorial priorities permit. Contributions ordinarily should not exceed 500 words in length, with a maximum of five references; they should be typewritten, double-spaced and submitted in triplicate. One Figure or Table can be printed.*

### Q Fever

*To the Editor.*—I read with interest the recent article by Sienko et al.<sup>1</sup> “Q fever: A call to heighten our index of suspicion.” The authors describe two cases of Q fever that appeared in a rural area in Michigan and present data showing a surprisingly high prevalence of antibody to *Coxiella burnetii* in goats and among farming families that own goats.

Even in an endemic area, physicians need to be reminded of the importance of Q fever. I found *C. burnetii* to be the second most common cause of pneumonia in a healthy young adult population in Laredo, Tex.<sup>2</sup> Most of my patients had no contact with farms or farm animals, and airborne dissemination of infective particles in an endemic area was thought to be responsible. Sienko et al<sup>1</sup> did not indicate the time of year that their cases appeared; presumably they were in the late spring after birthing, although the organism also disseminates with dry and dusty conditions in the late summer.<sup>2,4</sup> A report from Idaho<sup>3</sup> documented the winter, spring, and summer occurrence of Q fever reflecting twice-yearly birthing cycles at a local sheep research station.

One patient described by Sienko et al<sup>1</sup> had symptoms of acute prostatitis; a patient who was not included in my reported series had an identical presentation, and I found in my files a draft of a manuscript that never was published entitled, “Q fever presenting as acute prostatitis.” Neither of Sienko and colleagues<sup>1</sup> patients had patchy pneumonia nor abnormal liver function, findings that have often been present in previous cases. I am uncertain how to interpret the fact that one patient had a high antibody titer two weeks after the onset of symptoms, which declined fourfold in the ensuing four weeks of treatment. My patients all had fourfold increases in antibody

(although this may not have been entirely clear in the Table).<sup>2</sup>

One final point regarding therapy deserves mention. In recent years, probably due in part to increased awareness of legionellosis, physicians have increasingly prescribed erythromycin in the treatment of nonbacterial pneumonia. This tendency should be mitigated in areas where Q fever is a possibility. Erythromycin is not effective in treating infection due to *C. burnetii*, whereas tetracycline is.

DANIEL M. MUSER, MD  
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1. Sienko DG, Bartlett PC, McGee HB, et al: Q fever: A call to heighten our index of suspicion. *Arch Intern Med* 1988;148:609-612.

2. Musher DM: Q fever: A common treatable cause of non-bacterial pneumonia. *JAMA* 1968; 204:863-866.

3. Rauch AM, Tanner M, Pacer RE, et al: Sheep-associated outbreak of Q fever, Idaho. *Arch Intern Med* 1987;147:341-344.

4. DeLay PD, Lennette EH, DeOme K: Q fever in California: Recovery of *Coxiella burnetii* from naturally infected air-borne dust. *J Immunol* 1950;65:211-220.

### Science Education in the Preclinical Curriculum

*To the Editor.*—I agree with Alpert and Coles<sup>1</sup> that physicians often have an excessively narrow education and that they could benefit from more exposure to the humanities. However, this is best supplied as part of pre-medical liberal arts education. The two preclinical years are the only opportunity to instill the basic scientific knowledge at the heart of medical practice. The poverty of preclinical education results from too little attention to science rather than too much.

Much of my medical school experience was rote memorization. Laboratories and discussions of research papers had been largely eliminated, removing the students from direct exposure to the material. This appears to be a general trend. As a result, one finds that many students do not even go to class, relying on a transcription service to produce lecture notes that identify the material to be memorized. The preclinical curriculum is thus demoralizing for both students and faculty. An overemphasis on preparation for the National Boards is not primarily a response to the onerous requirements of the examination, but results from the lack of a coherent educational goal.

Although medical schools still require organic chemistry laboratory as part of premedical preparation, many schools have eliminated laboratories during preclinical training. Anatomy and physiology laboratories are far

more relevant to medicine than is organic chemistry. Science is more useful when concepts and methods are learned than when its results are simply accepted as sets of facts. There are several advantages to teaching science this way. First, a field of knowledge that is understood is retained better than one that is memorized. Second, some of the scientific views of today will be modified or replaced within the decade. If the practitioner is to use the discoveries of the future, he must know something of how these discoveries are being made, their limitations, and their potential applications. Third, and most importantly, medicine's conspicuous success over the past several decades has been due to discoveries in biochemistry, immunology, microbiology, and other basic sciences. Although there are virtues in the more humanistic approach of last century's doctors, no one would argue for returning to their style of practice.

As medical sophistication increases, there is a tendency to codify practice. Medical malpractice litigation contributes to this tendency with its demand for a clearly defined standard of care for every ailment. Clearly defined procedures are important for emergency and intensive care procedures but not suitable for most areas of medicine, where knowledge remains very uncertain. The retreat from science and scientific thinking in medical education contributes to excessive codification, since current approaches to medical problems are presented as if they were final answers. The physician who lacks a scientific viewpoint becomes a technician. He has decreased abilities to apply new ideas and to find the unexpected correlation that provides fresh insight. Even in day-to-day practice, informed decisions must constantly be made in situations where there is not a full understanding of underlying mechanisms or a sound foundation of empirical results. The more one understands of physiology and pathophysiology, the more informed these decisions become.

It may be that science and medicine have become so complicated that it is no longer possible to educate people both to be good doctors and to have a sound science background. If this is the case there may be a need for two or even three educational paths—for family practitioners and general internists, for technologically oriented specialists and subspecialists, and for biomedical clinician-researchers. Before considering such changes, it is worth considering the effects on the profes-

sion as well as on medical care and on progress. Furthermore, if the latter two groups are not to be phased out entirely, some medical institutions will need to orient themselves to their educational needs. Major medical centers with strong basic research departments have traditionally provided this kind of training. They should not stop now.

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1. Alpert JS, Coles R: The indigestible curriculum. *Arch Intern Med* 1988;148:277-278.

### Persistent Fever After Recovery From Granulocytopenia in Acute Leukemia

*To the Editor.*—In the recent article published in the January 1988 issue of the ARCHIVES, Talbot et al<sup>1</sup> reported that about 15% of 168 patients with acute leukemia had persistent fever immediately after recovery from chemotherapy-induced granulocytopenia. Although in this series the origin of fever was usually apparent, the authors emphasize that in three instances hepatic and/or splenic candidiasis produced protracted fevers that were difficult to diagnose. That article prompted us to describe two patients with acute lymphoblastic leukemia in whom prolonged fever after recovery from granulocytopenia was due to granulomatous hepatitis caused by *Candida*. In both patients the diagnosis was made by a laparoscopically-guided liver biopsy, and both showed complete resolution of infection with prolonged antifungal therapy.

*Report of Cases.*—CASE 1.—A 12-year-old girl with common acute lymphoblastic leukemia had a central nervous system leukemia relapse at 14 months from diagnosis. In the period of granulocytopenia following reinduction therapy, the patient developed fever without evident focus of infection and with negative bacteriologic studies. Empirical treatment with ceftazidime, amikacin, vancomycin, and amphotericin B was instituted, but no response was observed. On the 30th day following the beginning of fever flucytosine (5-fluorocytosine) was added to the regimen. Fifteen days later, the patient developed acute pain in the right upper quadrant of the abdomen, and a tender hepatomegaly was noted 5 cm below the right costal margin. At laparoscopy, multiple white nodules were seen on the liver surface, and the biopsy specimen of these lesions revealed large granulomas with central necrosis. The methanamine stain showed yeasts and pseudohyphae, which are characteristic of *Candida* species. Both the culture of liver tissue and the serologic studies for *Candida* species were negative. Because of the persistence of high fever, amphotericin B and flucyto-

sine were substituted by ketoconazole, which was followed by a transient disappearance of the hyperthermia. Finally, due to the reappearance of fever one week later, amphotericin B and flucytosine were given for ten additional weeks resulting on the definitive resolution of the fever. A second laparoscopy showed a normal hepatic surface, and the liver biopsy was also normal. Antifungal therapy was discontinued at five months from the beginning of fever when a total dose of 4.035 g of amphotericin B therapy had been given. However, the leukemia relapsed three months later and the patient died from septic shock following chemotherapy.

CASE 2.—A 17-year-old boy with common acute lymphoblastic leukemia had a second bone marrow relapse seven months after diagnosis. In the granulocytopenic period following chemotherapy, he developed fever, abdominal pain, and diarrhea. *Candida* species was isolated from stools and amphotericin B was added to previously instituted empirical antibiotic therapy with ceftazidime, amikacin, and vancomycin. Fifteen days later, because of persistence of fever flucytosine was also added, but no improvement was observed. At 45 days from the onset of fever a laparoscopy was performed, showing multiple white nodules on the liver surface. The biopsy specimen of one nodule disclosed large granulomas with central necrosis, in which yeasts and pseudohyphae characteristic of *Candida* species were observed. Culture of liver tissue was negative, and hemagglutination to *Candida* species was positive at a titer of 1/640. Ketoconazole (800 mg/d) was added to antifungal therapy, and because of disappearance of the fever both amphotericin B and flucytosine were discontinued. A second laparoscopy performed three weeks later showed a normal liver surface and the biopsy showed only hemosiderosis. However, a relapse of acute lymphoblastic leukemia was detected four weeks later and the patient subsequently died from massive gastrointestinal bleeding while being pancytopenic after chemotherapy. The patient had received a total dose of 3 g of amphotericin B. At necropsy, liver was enlarged with fatty change and hemosiderosis, but without evidence of candidiasis.

*Comment.*—The incidence of liver involvement in disseminated candidiasis varies from 4.8% to 59%,<sup>2,3</sup> hepatic candidiasis usually being part of the systemic infection. However, in recent years, cases with focal hepatic candidiasis have been recognized with increasing frequency.<sup>4,5</sup> The clinical presentation in our patients was similar to that reported by Talbot et al<sup>1</sup> and other authors,<sup>4,5</sup> and was constituted by the triad of persistent high fever after recovery from granulocytopenia, right upper quadrant or diffuse abdominal pain, and hepatomegaly. It is interesting to note that in

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