SPECIAL ARTICLE

Observations on Spiraling Empiricism: Its Causes, Allure, and Perils, with Particular Reference to Antibiotic Therapy

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In 1929, Sir Alexander Fleming [1] described the action of a fungal product, penicillin, on various bacteria. He noted that the ". . .toxicity to animals of powerfully antibacterial mould broth filtrates appears to be very low." During the hiatus between Fleming and Florey, Domagk discovered Prontosil, which was quickly applied in clinical practice. Lewis Thomas [2], then an intern at the Boston City Hospital, remembers ". . .the explosive news of sulfanilamide. . . .the astonishment when the first cases of pneumococcal and streptococcal septicemia were treated in Boston in 1937. The phenomenon was almost beyond belief." Safe and efficacious, penicillin, sulfanilamide, and subsequent antimicrobials have substantially extended our capability against bacterial diseases. The latest generations of cephalosporins and penicillins, the carbapenems, the monobactams, and the qūinolones (already fathering a second generation), offer an ever-broader spectrum of antimicrobial activity with minimal toxicity. Fleming, Domagk, and Florey could not have anticipated the proliferation of antibiotics that would follow their discoveries, nor would they have understood the profligate and injudicious use of these agents in modern therapeutics.

The imprecision of clinical practice establishes context; the litigious nature of our society unnerves; the absence of toxicity permits; and the sum of these encourages the incontinent, extemporaneous use of antimicrobial agents. Commenting on this issue, Dr. James E. Peacock [3] of Bowman-Gray School of Medicine averred: "One must strive to avoid spiraling empiricism." The term *spiraling empiricism* describes the inappropriate treatment, or the unjustifiable escalation of treatment, of suspected but undocumented infectious diseases. Empiricism and empirical therapy, defined as the carefully considered, presumptive treatment of disease prior to establishment of a diagnosis, often are necessary in the proper practice of medicine. On the other hand, ill-considered or inappropriate use of antibiotics, incurring unnecessary risk and expense, should be indicted and condemned. The difficulty lies in distinguishing reasonable or appropriate from unreasonable or inappropriate therapy.

We shall divide this systematic examination of empirical therapy into four parts: first, conceptual approaches to therapy; second, a statement of the rationale for empirical therapy; third, a review of the fallacies and perils of empiricism with illustrative cases; finally, a discussion of the proper place of empiricism in medical practice.

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A CONCEPTUAL APPROACH TO THERAPY

There are five primary interventions: observation, prophylaxis, empirical therapy, therapeutic trial, and specific therapy (**Table I**). At first glance, this classification might seem trivial, contrived, or worse, pedantic. Yet it provides a conceptual framework that clarifies therapeutic issues and places empirical therapy in its proper context.

In the first intervention, no specific therapy is initiated; only observation ("masterly inactivity") and supportive care are offered. Disease is present but is not immediately life-threatening, and no diagnosis is obvious. Clearly, a change is warranted if avoidable complications might arise from this type of intervention. The evaluation of a fever of unknown origin often follows this approach.

The second form of therapy is preventive or prophylactic. No disease is present. The potentially pathogenic target organisms may be in the environment, i.e., skin, mouth, or colon. Brief, selective therapy is given to prevent the development of a significant infection by these organisms, the underlying assumption being that the risk of acquiring the disease outweighs the risk of therapy itself. Preoperative antibiotic therapy for patients undergoing colon surgery exemplifies this approach.

The third form of therapy is empiric; infection is suspected, but unproven, and the patient would be placed at greater risk by observation than by treatment. The primary objective is to cure a presumptive disease. As a secondary gain, response to therapy supports the presumptive diagnosis of infection (although it must be remembered that responses may be apparent, not real). Treatment should be chosen to cover the likely diagnoses, of which there may be several. Broad-spectrum antibiotic therapy in the febrile, neutropenic patient typifies this form of therapy.

Fourth, related to the concept of empiric therapy but of much narrower scope and applicability, is the therapeutic trial. This involves a specific treatment of predetermined duration, whose primary objective is to help confirm a suspected diagnosis. A common example is treatment with isoniazid and ethambutol for six weeks or more in suspected tuberculosis. Rifampin should not be substituted for ethambutol because it has broad-spectrum antimicrobial activity. Note, on the other hand, that rifampin would be entirely appropriate if this were *empiric* treatment for tuberculosis (see previous section). Another example is penicillin plus streptomycin for two weeks or more for suspected, but culture-negative, endocarditis. In a therapeutic trial, the drugs used should be as selective as possible and treatment should be continued for the full, predetermined duration unless serious toxicity occurs or a definitive diagnosis is established.

The fifth intervention is specific therapy, the selective administration of antimicrobials for a known dis-

TABLE I

Features and Objectives of the Various Therapeutic Options with Examples

Therapeutic Options	Objective(s)	Duration	Classical Example	Appropriate Drug(s)
Observation • Diagnosis unknown • No specific therapy • Symptomatic therapy • Do no harm	Identify disease prior to therapy	Variable, according to progress	Fever of unknown origin	None
Prophylaxis • Target organism(s) • Greater risk from disease caused by target organisms	Prevent development of infection	Very brief	Subacute bacterial endocarditis Rheumatic fever Meningococcal disease Preoperative colon surgery	Penicillin V Benzathine penicillin Rifampin Oral neomycin plus erythromycin
Empiric therapy • Infection suspected, but not proven • Patient too ill for observation only • Adjust regimen if diagnosis proven	1°:Cure disease 2°:Infer presence or absence of disease from response	Variable, according to progress	Neutropenia, fever Pneumonia Gram stain-negative meningitis	Ticarcillin plus tobramycin Erythromycin Cefotaxime
Therapeutic trial • Specific etiologic organisms suspected but not proven • Specific selective therapy to make diagnosis • Predetermined duration of therapy	1°:Diagnosis of disease 2°:Cure disease	Predetermined, usually two weeks or more	Tuberculosis Subacute bacterial endocarditis Rheumatic fever Temporal arteritis	Isoniazid plus ethambutol, six weeks Penicillin plus gentamicin, two weeks Aspirin, two weeks Prednisone, six weeks
Specific therapy • Specific etiologic organisms proven or highly suspected • Only one target organism	Cure disease	Variable, according to disease or progress	Erysipelas Pneumocystis Scrub typhus	Penicillin Pentamidine Doxycycline

ease, e.g., penicillin for pneumococcal pneumonia. Ascertainment of a diagnosis usually allows a switch from empiric to specific therapy. Note that this may simply be a conceptual change that does not necessitate a change in the treatment regimen the patient is already receiving.

Clearly, empiric therapy is heavily utilized. We recognize the necessity for empiric therapy in the practice of medicine, but we must also acknowledge its potential for abuse. The causes of this abuse are diverse and deeply rooted, its cost substantial, and its correction difficult. A more extensive examination of the rationale for empiric therapy, with an indictment of spiraling empiricism, follows.

EMPIRICISM: AN APOLOGY

"Principiis obsta; sero medicina paratur / Cum mala per longas convaluere moras" (Resist at the start / Medicine comes too late when disease is increased through long delay), wrote Ovid [4] in *Remedia Amoris*. Ovid captured, in unintentional aphorism, the principal justification for empiric therapy. The immediacy of suffering, the desire to alleviate distress, the desire for action, the fear of errors of omission, and the corresponding fear of litigation favor impulsive therapeutic activity over accurate diagnosis and specific therapy. Hippocrates [5] recognized the same problem among physicians of his day when he warned: "In acute diseases employ drugs very seldom and only in the beginning. Even then, never prescribe them until you have made a thorough examination of the patient."

Empiric therapy is, similarly, that which might be most subject to overuse; the determination of a presumptive diagnosis or the enumeration of diagnostic possibilities in the febrile patient frequently invokes infection. Severity of illness, the potential for deterioration without treatment, and the desire to relieve distress are imponderables. William Osler [6] described this dilemma lucidly:

> Our study is man, as the subject of accidents or diseases. Were he always, inside and outside, cast in the same mould, instead of differing from his fellow man as much in consititution and in his reaction to stimulus as in feature, we should ere this have reached some settled principles in our art.

It is from this perspective that we present some disturbing cases of spiraling empiricism, noting the misconceptions or fallacies found in each. A summary of these fallacies is found in **Table II**. Our cases relate to known or suspected infectious diseases, though examples might easily be found in other specialties.

SPIRALING EMPIRICISM: CASES, COMMENTS, AND FALLACIES

Patient 1

A 53-year-old farmer was admitted in mid-September with fever, wheezing, thrombocytopenia, diarrhea, and rash. He had consulted his personal physician four days previously because of cough and chills and had

been given cephalexin. He presented to an emergency room with a temperature of 39.7°C, pulse 140/minute, respirations 30/minute, and blood pressure 110/80 mm Hg. Physical examination was notable for bilateral wheezes and rhonchi and a macular rash over the trunk and legs. The white blood cell count was 12.3 × 10^9/L, with 34% neutrophils and 59% band forms. The platelet count was 80.8 × 10 ^{9}/L. Urinalysis showed four to six white blood cells and two to three red blood cells per high-power field and 1+ albumin. Stool specimens cultured for ova and parasites grew *Strongyloides stercoralis*.

The patient was admitted at 9:00 AM and culture specimens were obtained. At 11:00 AM, therapy with cephapirin was started. His temperature rose to 40.0°C, and his mental status deteriorated. At 9:15 PM, his antibiotics were changed to erythromycin and trimethoprim/sulfamethoxazole; at 11:15 PM, tetracycline was added. At 1:00 AM on the second day of hospitalization, an infectious diseases consultant recommended that treatment be changed to chloramphenicol and gentamicin. Results of a lumbar puncture were normal. His maximum temperature on Day 2 of hospitalization was 39.4°C. On the third day of hospitalization, clindamycin was substituted for chloramphenicol by his physicians "for better anaerobic coverage"; his maximum temperature was 40.7°C. The Department of Infectious Diseases recommended the addition of tetracycline on Day 4. The patient had a maximum temperature on Day 5 of 38.9°C; erythromycin was re-introduced. Results of a direct fluorescent antibody test for *Legionella pneumophila* were negative. By the seventh day of hospitalization, he was afebrile. Doxycycline was substituted for tetracycline, and gentamicin was stopped. Clindamycin was stopped on Day 9. On Day 15, all antibiotics were stopped; the patient was discharged in good health. Two weeks later, results of acute and convalescent complement-fixing antibody titers to *Rickettsia rickettsii* were available and they showed an increase from 1:64 to 1:4,096. All other cultures and serologic tests, including antibody to human immunodeficiency virus, were negative.

COMMENT: The haphazard management of this case of Rocky Mountain spotted fever demonstrates a number of fallacies:

Fallacy 1: "Broader is better."

Fallacy 2: "Failure to respond is failure to cover."

Fallacy 3: "When in doubt, change drugs or add another."

Chloramphenicol or tetracycline would have sufficed. Little was gained by the antimicrobial equivalent of "stone soup"; in fact, during the welter of different antimicrobials, omission of one critical antibiotic almost occurred.

Changes in empiric therapy should be made sparingly, and only when there is new information to justify a change. In general, empiric therapy is broad-spectrum; usually three to five days should be allowed to pass before an assessment of response is made. As Virgil [7] wrote: "Tu ne cede malis, sed contra audentior ito" (Yield not to misfortune, but go on more bravely).

Patient 2

A 27-year-old woman with systemic lupus erythematosus was admitted with ascites. The patient had a three-month history of idiopathic ascites that had recently worsened. Perianal vesicular lesions, Tzanck-smear positive, were treated with acyclovir. Gastrointestinal bleeding occurred and she required transfer to the intensive care unit for hypotension. Upper endoscopy revealed a small esophageal ulcer; biopsy results were not consistent with vasculitis. Ceftazidime, vancomycin, and gentamicin were started for presumed "sepsis." *Clostridium septicum* was isolated from a blood culture. Her condition responded to therapy with antibiotics, packed red cells, fresh frozen plasma, and platelets, and she was transferred back to her room; massive lower bowel bleeding again ensued. She was transferred to the intensive care unit where transfusions, gentamicin, and clindamycin were given. She was febrile to 38.5°C through much of her stay in the intensive care unit. Her antibiotic regimen rapidly escalated to include clindamycin, tobramycin, ceftazidime, vancomycin, amphotericin B, and acyclovir. Her intestinal bleeding continued and was finally controlled by total colectomy. This was complicated by postoperative fever and ileus. Therapy with clindamycin and gentamicin was again started; vancomycin was added by the infectious diseases consultant. Computed tomograms of the abdomen showed a massive retroperitoneal hematoma; small bowel obstruction occurred, and the patient was again taken to surgery. Lysis of adhesions and drainage of the hematoma were followed by defervescence. All cultures, including those of the hematoma, showed no growth. Her antibiotics were discontinued.

TABLE II

Fallacies in Antibiotic Therapy

I. Broader is better
II. Failure to respond is failure to cover
III. When in doubt, change drugs, or add another
IV. More disease(s), more drugs
V. Sickness requires immediate treatment
VI. Response implies diagnosis
VII. Bigger disease, bigger drugs
VIII. Bigger disease, newer drugs
IX. Antibiotics are non-toxic

COMMENT: This fascinating case is typical of the plight of the patient subject to an empirical antibiotic spiral. In addition to Fallacies 1, 2, and 3, this case illustrates a fourth.

Fallacy 4: "More disease(s), more drugs."

The impressive collection of antibiotics probably did little for the patient's disease, which was cured by colectomy, relief of intestinal obstruction, and drainage of her retroperitoneal hematoma. Hippocrates [8] is succinct: "What drugs fail to cure, iron (the knife) cures. . . ."

Patient 3

A 27-year-old man with a T-cell lymphoproliferative disorder and pulmonary infiltrates was admitted with loss of vision in the right eye. The patient had received combination chemotherapy for his hematologic malignancy with some improvement in his pulmonary infiltrates. He was seen on the morning of admission by an ophthalmologist who diagnosed retinitis, most likely caused by *Toxoplasma gondii*. Empiric antibiotic therapy, consisting of pyrimethamine plus sulfadiazine, was started. He received further combination chemotherapy and became neutropenic. Whitish pharyngeal ulcers appeared and were treated

with acyclovir and amphotericin B 50 mg/day for possible herpes simplex and *Candida*. He became febrile, so ceftazidime was started. Persistent fever, despite negative results on blood, urine, and sputum cultures, prompted the addition of vancomycin, then amikacin. Acyclovir was discontinued. His pulmonary infiltrates worsened. Trimethoprim/sulfamethoxazole was added for possible *Pneumocystis carinii* pneumonia. Bronchoscopy was performed and the results were negative for fungi and *P. carinii*, although an unconfirmed note in the chart described the isolation of an *Aspergillus* species. Trimethoprim/sulfamethoxazole was replaced by flucytosine. His creatinine level began to increase. Neutropenia resolved over three weeks. The patient complained of progressive loss of vision and pain in the right eye. Serial funduscopic examinations documented progression of the retinal lesion. A vitreal aspirate showed branched, septate hyphae, but cultures of the vitreous yielded negative results.

COMMENTS: This unfortunate case illustrates further perils of empiric therapy. The initial diagnosis of retinal toxoplasmosis began the spiral, followed by a string of empiric agents for the treatment of fever and neutropenia. The diagnosis of aspergillosis in a neutropenic patient should be pursued aggressively. There are data to support the notion that early treatment may improve survival; moreover, aspergillus infection may progress despite empiric amphotericin B and the return of neutrophils [9]. Empiric antibiotic therapy has traditionally been considered superior to expectant therapy [10–13] in the management of the febrile neutropenic patient; more recent studies, however, suggest a much lower incidence of bacteremic disease than previously appreciated [12,13], as well as disagreement over the preferred regimen [13]. In one interesting study, empiric vancomycin therapy yielded no better results than specific vancomycin therapy instituted only after the diagnosis of infection in persistently febrile, neutropenic patients [14]. Despite the absence of a significant difference in case fatality rates between patients randomly assigned to empiric or specific vancomycin for persistent fever and neutropenia, Karp *et al* [15] recommended empiric vancomycin because of a reduction in febrile days and amphotericin B requirement. The studies justifying the empiric use of amphotericin B should, similarly, be viewed critically [16,17].

Patient 4

A 35-year-old woman living in a southern state was admitted in early January with headache, dizziness, and bilateral facial palsies. She had no history of outdoor activity, recent travel, or tick bites. Two months previously, she had had a left Bell's palsy that responded partially to prednisone. Shortly before admission, she experienced the acute onset of right facial tingling and paresis. Neurologic examination revealed right-greater-than-left palsy of cranial nerve VII, and involvement of cranial nerves IX, X, and XII. Computed tomograms and magnetic resonance imaging of the head were normal. Cerebrospinal fluid (CSF) examination revealed a normal glucose level, an elevated protein level, and a white blood cell count of 4/mm^3. A repeat lumbar puncture showed a white blood cell count of 10/mm^3. Results of cultures of the CSF for bacteria, fungi, and mycobacteria were negative. The CSF VDRL and cytologies were negative. The chest radiograph showed hilar adenopathy without parenchymal disease. Results of a tuberculin skin test were negative, with a positive control. An infectious diseases consult was contacted to consider the advisability of high-dose penicillin (12 to 20 million units per day) for Lyme meningitis. Although Lyme meningitis was thought to be an unlikely diagnosis by the consultant, high-dose penicillin therapy was instituted. The patient showed improvement, with resolution of her headache and gradual improvement of her facial nerve palsies. Bronchoscopy was urged despite this "successful" trial and revealed non-caseating granulomata; high-dose pencillin was halted, and prednisone therapy was initiated for presumed sarcoidosis of the central nervous system.

COMMENT: This patient with central nervous system sarcoidosis was treated with high-dose penicillin for possible Lyme meningitis.

Fallacy 5: "Sickness (especially infection) needs immediate treatment."

Fallacy 6: "Response implies diagnosis."

The epidemiologic and clinical features of Lyme meningitis are incompatible with her clinical presentation and a coincidental "response" to empiric therapy nearly obscured the diagnosis. This case illustrates the delay of diagnostic tests by a seemingly successful empiric trial of antibiotics. The notorious fallacy, "Post hoc, ergo propter hoc" might also be appropriately recalled.

Patient 5

A 70-year-old woman with a history of diabetes and hypertension was admitted for an acute anterior wall myocardial infarction. During emergency cardiac catheterization, ventricular fibrillation occurred, and an intra-aortic balloon pump was inserted. Upon return to the cardiac care unit she was hypoxic, hypotensive, and febrile. A chest radiograph was consistent with pulmonary edema, though pneumonia could not be excluded. Swan-Ganz catheter readings were said to show "septic numbers," i.e., a low systemic vascular resistance, a somewhat elevated cardiac output, and a low arterial-venous oxygen difference (also consistent with balloon pump physiology). She was given ceftazidime and clindamycin for presumed septicemia and aspiration pneumonia. Persistent fever and leukocytosis soon led to the addition of vancomycin. Shortly thereafter, "better therapy" was thought to be needed, so ticarcillin-clavulanic acid and tobramycin were added. Defervescence, decreased white blood cell count, and improved oxygenation occurred slowly, although her cardiac and neurologic status failed to recover. Candidal fungemia and septicemia complicated her course. After discussion with her family, support was gradually withdrawn and she died.

COMMENT: The critically ill patient is often subjected to an empirical treatment spiral, moving in a direction, it has been wryly observed, antiparallel to the downward physiologic spiral.

Fallacy 7: "Bigger disease, bigger drugs."

Fallacy 8: "Bigger disease, newer drugs."

Fallacy 9: "Antibiotics are non-toxic."

This case suggests that ideas regarding the relative strengths and weaknesses of antibiotics are not confined to their spectrum, mode of pharmacologic activity, or specific toxicity (such as salt load) but extend to an abstract sense of "power." Again, not enough time

was given for a response to therapy to occur; it is in the acutely ill patient with multiple organ system failure that response to therapy is, as one might expect *a priori*, least rapid.

It might further be argued that antimicrobial therapy itself contributed to this patient's decline—worsening of her heart failure by ticarcillin (5 mEq sodium per g) and candidemia favored by broad-spectrum antimicrobials.

COMMENTS

Beeson [18] summarized the rapid, salutary progress in antimicrobial therapy with this observation:

> It is not surprising to find that infectious diseases is the field in which the most spectacular improvements in prevention and treatment have occurred in recent decades.

Refinements in antimicrobials have broadened coverage and improved therapeutic ratios, but as Dubos [19] pointed out in 1958, the intelligent and selective use of antibiotics is frustrated by the imperfection and imprecision of medical practice. The proliferation of broad-spectrum, non-toxic antimicrobials has increased the level of imprecision. We have abandoned the specific and parsimonious use of antimicrobials for the complacent security of the "cefs-du-jour." The magic bullet of Ehrlich, an antimicrobial "smart" weapon, selective and specific, has paradoxically become a blunderbuss, aimed generally and scattering pellets widely—over gram-negative rods and gram-positive cocci alike, perhaps anaerobes, occasionally enterococci, and hopefully, even the dreaded *Pseudomonas*.

Unfortunately, spiraling empiricism is both pervasive and unquestioningly accepted. Studies of empiric therapy in febrile neutropenic patients [10,12], good and bad, have been canonized, and the results have been extended uncritically to all "immunocompromised hosts." Prospective payment systems, with their emphasis on procedures and treatments, discourage therapeutic parsimony and encourage (or at least do not yet forbid) the vague and unproven diagnoses that are best suited for empirical polypharmacy. One member of the pharmaceutical industry responded with an "Anencephlin® guarantee," promising payment of additional antibiotic costs if a patient treated initially with their cephalosporin failed to meet diagnosis-related-group specifications for discharge. House officers would sooner use a first-generation cephalosporin plus an aminoglycoside than penicillin for community-acquired pneumonia [20], a circumstance advancing the thesis that fashion and marketing forces, not science, shape clinical practice [21]. Within an intensive care unit, gravity of illness amplifies the effects of delay and presses for preemptive, urgent empiricism, but the selection and manipulation of therapy can sometimes justly be criticized (see Patients 2 and 5). The intensive care unit mentality, which treats all illness as life-threatening, favors therapy over careful consideration of diagnostic maneuvers. Finally, while the legal consequences of therapeutic excess are insubstantial, the risk of therapeutic economy abuts, too nearly, the liability of undertreatment. The potential for, and tendency toward, spiraling (as opposed to appropriate) empiricism appears disturbingly pervasive—reinforced by fashion, compensation, and litigation.

Empiricism is not "the last refuge of the scoundrel" (Dr. Johnson) but it is a necessary component of the medical art. However, several points concerning the proper use of empiric antimicrobials should be made. First, consider the therapeutic alternatives; is observation without treatment a viable alternative? Second, therapy should be undertaken with a clear, preferably written, purpose: prophylactic, empiric, therapeutic trial, specific. Third, treatment is no substitute for diagnosis. Apparent responses to empiric therapy should be critically assessed to determine causality—that a strict relationship between therapy and response can be made. Fourth, response to empiric therapy must be assessed cautiously; appropriate time periods should be allowed to elapse before making changes in antimicrobials. Fifth, antimicrobials should be viewed in the context of the specific illness being treated, with an appreciation of the expected response to therapy. Sixth, antimicrobials should be used with due allowance for their various spectra and toxicities.

Ober [22] recently described the "tar-baby effect"—the quagmire of diagnostic tests in which clinicians may become entrapped. It might be appropriate to consider spiraling empiricism as the therapeutic parallel to Ober's tar-baby phenomenon. Central to the concept of empirical treatment is uncertainty regarding diagnosis. When a truly attributable response occurs, a diagnosis may be inferred; the danger lies in overinterpreting responses related temporally, but not causally, to the intervention. Spurious responses first obfuscate, then delay, appropriate diagnosis and therapy. Uncertainty of diagnosis is most acutely experienced later when indeterminate or marginal responses follow empiric therapy. Partial, but inadequate, treatment may coincidentally mask or subtly alter the manifestations of the disease. At this point, the question of proper treatment often becomes difficult: to add or to substitute drugs? The related issue of termination of therapy, more particularly the termination of marginally effective therapy, frequently confronts the empiricist and defies facile resolution. In the words of the Sybil: ". . .sed revocare gradum, superasque evadere ad auras / Hoc opus, hic labor est" (But to recall your steps and to escape to the upper air / This is the work, this the toil) [23]. If legitimate empirical treatments are attended by such difficulties, how much more might the thoughtless improvisation of spiraling empiricism serve to confound or entangle?

Osler's [7] comment that the "practice of medicine is an art, based on science" underscores the dichotomy, and the dilemma, of medical science. Empiric therapy at its best is set between the Scylla of unnecessary delay and the Charybdis of therapeutic voyeurism. Knowledge of the science of medicine and the natural history of diseases should temper and complement the art; without that knowledge, the practitioner ". . .flounders along in an aimless fashion, never able to gain any accurate conception of disease, practising a sort of popgun pharmacy, hitting now the malady and again the patient, he himself not knowing which" [24]. The clinician, neither rogue nor quack, is confronted daily by questions of therapy, diagnosis, and humanity, each a challenge to the adequacy of his or her art and clinical science.

If the toxicities and efficacy of popgun pharmacy have been favorably altered by modern pharmaceuti-

cal science and licensing requirements and if the intemperate use of antimicrobials persists (as likely it shall), the probability of "hitting now the malady" should reasonably continue to satisfy "the conscience of the multitude" (Gibbon). If, however, these technologic improvements occur without the benefit of similar improvements in the "accurate conception of disease" or diagnosis, the possibility and likelihood of unnecessary, indiscriminate therapy increases; misconception speciously reinforces the impression of clinical experience; and the spiral is perpetuated. The poetry of Yeats [25] metaphorically depicts this vicious, empirical spiral:

> Turning and turning in ever-widening gyre
> The falcon cannot hear the falconer;
> Things fall apart; the centre canot hold.

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