Cryptococcosis

WHEN A PATIENT IS DYING of a disease, the rarity of the disease offers scant consolation to the patient or physician. And somehow the rarity seems relatively insignificant to both. The inherent tragedy is compounded when death occurs from a curable, albeit rare, disease. Perhaps one should compute a *significance factor* for rare diseases, which would be the product of the incidence times the percent mortality untreated times the percent cured by appropriate treatment. Thus, the significance factor for cryptococcal meningitis would be very roughly 0.2 cases per 100,000 people per year times 100 (percent fatality untreated) times 55 (percent cured with appropriate therapy). From this vantage point, the special conference on cryptococcosis in this issue is seen not as an academic exercise in minutiae but as a useful guide for busy practitioners.

For those physicians using guides like this to assist them down the entire road of diagnosis, treatment and follow-up, a useful supplement would be a "Guide to Common Pitfalls." For cryptococcal meningitis, the list of things physicians most often do not know might include the following: (1) several milliliters of cerebrospinal fluid (CSF) may need to be cultured to grow *Cryptococcus neoformans;* (2) weekly CSF fungal cultures are invaluable in deciding when to end therapy; (3) when amphotericin B therapy is changed from every day to every other day, the dose must be doubled; (4) flucytosine dosage must be reduced in azotemic patients to prevent severe leukopenia, thrombocytopenia and enterocolitis, and (5) routine posttherapy lumbar punctures and computerized axial tomographic (CAT) scans may detect relapse or hydrocephalus, respectively, before permanent sequelae occur.

Since the time the conference reported in this issue was held, the collaborative cryptococcal meningitis therapeutic trial has been published.[1] Efficacy of the two-drug regimen in this study can be seen easily, but the 30 percent incidence of flucytosine toxicity should not be overlooked. Although these toxic reactions were not life-threatening in study patients, fatalities have been reported in the literature. There is still no easy regimen for treating patients with cryptococcal meningitis. Miconazole has proved relatively nontoxic, but there is no convincing evidence that the drug is effective at all in cryptococcosis. For the present, physicians caring for patients with cryptococcosis must remain tormented by the fact that this disease is curable yet the day-to-day management is often extraordinarily difficult. This predicament, of course, is not new:

> Diseases desperate grown
> By desperate appliances are relieved,
> Or not at all. (*Hamlet* IV:iii,9)

JOHN E. BENNETT, MD
Head, Clinical Mycology Section, LCI
National Institute of Allergy and Infectious Diseases
Bethesda, Maryland

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Unanswered Questions About Tubulo-interstitial Nephropathies

TWENTY YEARS AGO the Medical Staff Conference by Dr. Cogan, which appears elsewhere in this issue, would have been entitled "Chronic Pyelonephritis" and a bacterial cause for the resulting chronic interstitial scarring would have been the only theme discussed. Fortunately, new knowledge has broadened both the known and suspected causes of tubulo-interstitial disease, and these are appropriately emphasized by Dr. Cogan's discussion.

That tubulo-interstitial disease is a significant entity can be appreciated from reviews of the various causes ascribed to end-stage renal disease. At present it is estimated that in a quarter to a third of patients with end-stage renal disease who are evaluated for renal replacement therapy a diagnosis of chronic interstitial nephritis eventually can be made. Of equal importance is the number of drugs that have been identified as causing acute interstitial nephritis through the immunologic mechanism described by Dr. Cogan. This list grows each year and, in addition to the penicillin and penicillin-like compounds, includes the thiazide diuretics, furosemide, phenindione, sulfonamides, diphenylhydantoin, allopurinol, azothioprine and rifampin.

However, when one examines the various

causes for chronic interstitial nephritis, the evidence supporting an immunologic basis is less compelling. A feature common to many of the proposed causes of chronic tubulo-interstitial disease is the associated renal medullary damage. This is best recognized in conditions such as analgesic nephropathy, urinary tract obstruction with reflux, diabetic nephropathy, sickle cell disease, Balkan nephropathy and various other diseases of the kidney. The contribution of bacterial infection to the incidence of chronic interstitial disease is in dispute. "Present evidence indicates that bacterial infections of the urinary tract can produce serious renal disease only when associated with other conditions that are by themselves damaging to the kidney and act to increase the susceptibility of the kidney to infection"; so state Freedman and Andriole.[1] For completeness, several of the congenital metabolic defects have associated renal lesions which are tubulo-interstitial in character—Wilson disease, the Alport syndrome, primary hyperoxaluria and cystinosis. Finally, gouty nephropathy, nephrocalcinosis, hyperphosphatemia, heavy metal poisonings (chronic), disseminated intravascular coagulopathy and radiation nephritis all result in tubulo-interstitial disease of varying severity.

By and large, as pointed out by Dr. Cogan, treatment has remained symptomatic, although a recent report from Galpin and co-workers[2] suggests that short-term high dose steroid therapy may speed the recovery of renal function following drug induced acute tubulo-interstitial nephropathy. The problem of analgesic nephropathy continues to be distressing because it is a totally preventable entity provided it is recognized early and the patient will abstain from further analgesic abuse. Often the psychological dependence defeats attempts to withdraw the analgesic and there are multiple examples in every nephrologist's practice of patients who have received renal transplantation or who are undergoing dialysis for a disease for which we not only understand the cause but also the means of prevention.

Much information concerning tubulo-interstitial disease has been collected in the last 20 years, but unanswered questions still remain. Are many of the cases of chronic tubulo-interstitial disease examples of recurrent acute episodes that are subclinical? What is the role of environmental exposure in causing interstitial disease of the kidney? What explains the pronounced geographic discrepancies in the worldwide distribution of analgesic nephropathy? It is hoped that when a Medical Staff Conference in THE WESTERN JOURNAL OF MEDICINE next addresses tubulo-interstitial nephritis, some of these questions can be answered.

GEORGE A. PORTER, MD
Professor and Chairman
Department of Medicine
University of Oregon
Health Sciences Center
Portland, Oregon

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Discrimination in High Places

YET ANOTHER INCREASE in the Social Security tax in January of this year again focuses attention on the behemoth which seems to take so much from us and to give so little in return. Its promise as a retirement system providing lifelong security is proving to be a tragic disappointment if not a hoax to those who depend upon its retirement benefits to survive in an economy of runaway inflation. Medicare has become a generally welcome benefit equally for rich and poor. The role of Social Security welfare has been the subject of much criticism. Its principle is that those who are working are taxed to provide benefits to retirees and to other beneficiaries who are in need of one or another kind of welfare aid. The result is something of a hodgepodge of earned and unearned benefits financed by some but not all who work.

It surely seems that if the social security provided by this system with its ever increasing tax were good for some Americans it would be good for all and that all who work should be required to participate. But this is not the case. Those who should know best, the federal employees, who number among the millions, have succeeded in remaining outside the system for all these years and pay no Social Security tax. It would seem that this is something like discrimination in high places, if what is good enough for the public is not good enough for those whom the public pays to work in the federal government. It sticks in this craw.

—MSMW