

Colchicine for Familial Mediterranean Fever: The Stephen E. Goldfinger Story

This is a summary of Dr. Stephen Goldfinger's personal account of the discovery of colchicine as a treatment for familial Mediterranean fever.

Prepared by Janine Jagger (January, 2014)

The first step in Dr. Goldfinger's journey along the historical path of FMF discovery was taken during his preparation for a medical residency interview at Massachusetts General Hospital (Harvard) in Boston, Massachusetts. Expecting to be interrogated about his knowledge of exotic rare diseases, FMF was one of several such diseases that he committed to memory. Although the opportunity to flaunt this obscure knowledge did not arise during the interview, he was nevertheless accepted into the program at Massachusetts General where he excelled and subsequently built his career, and where he continues to practice today.

It was about a decade after his residency interview in the mid-1960s that Dr. Goldfinger first put his knowledge of FMF to use. As a junior member of the clinical staff he saw his first FMF patient; a young woman referred to him by a psychiatrist. The patient was deeply depressed; her life was being destroyed by recurrent attacks of excruciating peritonitis and fever. Being aware of several therapies that had been tried but had failed to stem the brutal attacks, Dr. Goldfinger had to tell the young woman that he had nothing to offer her except narcotics.

Shortly afterwards, while at an out-of-town meeting, Dr. Goldfinger received an urgent message that his FMF patient had attempted to take her life. She remained hospitalized in a coma for four days, but survived. Desperate to find an effective treatment for his patient, Dr. Goldfinger raised the question among some colleagues that he joined at lunch in the hospital cafeteria, asking if they had heard of any treatments for FMF – and he got a surprising response. Colleague, Dr. Guillermo Sanchez, told him about one of his gout patients who also had FMF – and that the patient's FMF attacks ceased when placed on colchicine for gout. Dr. Goldfinger recounts, "I immediately began the young woman on daily colchicine. She had no further attacks! Sparked by this unbelievable happening, I sought out other FMF patients to try them on colchicine."

Dr. Goldfinger searched and found 5 FMF patients and was able to treat them with colchicine for 127 combined

months (average per patient, 25 months). The pre-colchicine attack frequency averaged one per month (expected number of attacks = 127). Only 4 attacks occurred in the colchicine treated patients.

Dr. Goldfinger submitted the results of his trial to the New England Journal of Medicine (NEJM) where it was promptly rejected because it was not a double blind clinical trial, and therefore did not meet the journal's standard for scientific rigor. [editorial note: *a double blind clinical trial under the circumstances would have been out of reach – it would have required starting over with the elusive task of recruiting even more patients and at least a couple more years to carry out the study and another year for submission to a journal and publication*]. Finally, NEJM agreed to publish a "letter" which sets a lower bar for scientific rigor.

The humble letter, bearing the title, "Colchicine for Familial Mediterranean Fever," by sole author, Stephen E. Goldfinger, published in the New England Journal of Medicine, December 21, 1972, would remain the historical touchstone of colchicine therapy, saving lives and restoring the health of thousands upon thousands of FMF patients worldwide – and will continue to do so for generations of descendants of today's patients.

Dr. Goldfinger provided a footnote to the story. He later learned that Dr. Kurt Block, had been a consulting immunologist for Dr. Sanchez' historic patient who had both gout and FMF, and that Dr. Block had suggested at that time that colchicine should be used to treat FMF. In reference to Dr. Block's earliest observation, Dr. Goldfinger added, "He deserves much of the credit."

[editorial note: *It is not enough to simply make a clinical observation for a new therapy to be accepted and widely adopted. It must be tested under credible circumstances on multiple patients and pass peer review for publication in an established medical journal. The circumstances that Dr. Goldfinger faced were challenging due to the scarcity of FMF patients in the Boston area. With scant material to work with he nevertheless cleared the hurdles one by one to bring his findings to a widespread medical audience. Later there would be a clinical trial that would confirm his original observations on those first five patients - by which time colchicine would already be adopted as standard treatment for FMF.*]

COLCHICINE FOR FAMILIAL MEDITERRANEAN FEVER

To the Editor: Five patients with well established familial Mediterranean fever have been placed on chronic therapy with colchicine, 1 to 3 tablets per day. All of them had prior severe disabling attacks occurring at intervals ranging from every six to 10 days to every six weeks (Table 1). Depression and work-absenteeism characterized their lives. Numerous therapeutic modalities had been unsuccessful.

After they had been on daily colchicine, only four full-blown attacks were noted in 127 patient months of treatment. Two of these occurred shortly after colchicine was temporarily discontinued. A

Table 1. Clinical Features and Response to Colchicine Therapy of Five Patients with Familial Mediterranean Fever.

FEATURE	CASE No.				
	1	2	3	4	5
Age (yr)	42	26	47	43	27
Sex	M	F	F	M	M
Ancestry	Hebrew	Hebrew	Syrian	Hebrew	Hebrew
Duration of illness (yr)	27	20	41	20	4
Serum uric acid (mg/dl)	6.1-7.1	4.0	3.1	8.2	6.4
Attack frequency before colchicine	3-4 wk	4 wk	4 wk	6-10 days	6 wk
Duration of colchicine therapy (mo)	54	27	20	16	10
No. of attacks after colchicine instituted	1*	2	0	0	1*

*Attack occurred shortly after patient discontinued colchicine.

noteworthy improvement in life style was reported by each patient in euphoric terms. No adverse effects were encountered.

Evidence cited by Malawista¹ and Wallace² strongly suggests that in gout, colchicine acts by interfering with the phagocytic role of polymorphonuclear leukocytes exposed to microcrystals of sodium urate. It is intriguing that effusions from patients with familial Mediterranean fever have been observed to contain polymorphonuclear leukocytes showing marked phagocytic activity and spherical inclusion bodies interpreted as consisting of triglycerides.³ Interference with phagocytosis in both diseases might break a cycle of inflammation at its early inception, with resultant protection from clinical sequelae.

The beneficial effect of colchicine reported in this group of five patients with familial Mediterranean fever must be interpreted with caution. Observers have noted the viscissitudinous course of this illness, and a full appreciation of the role of colchicine in its treatment will require a double-blind study of a large number of patients. Until this can be accomplished, however, the use of oral colchicine in low dosage seems sufficiently benign to be warranted as a therapeutic trial in other patients with disabling attacks of familial Mediterranean fever.

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3. Sohar E, Gafni J, Pras M, et al: Familial Mediterranean fever. *Am J Med* 43:227-253, 1967