THE FUNGAL ETIOLOGY OF GOUT AND HYPERURICEMIA: THE ANTIFUNGAL MODE OF ACTION OF COLCHICINE

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ABSTRACT

The concept of a fungal/mycotoxin etiology of gout/hyperuricemia in humans was first reported by Costantini (1989) (1). Gout and/or hyperuricemia have been induced in animals by the fungal species Ustilago maydis, Chaetomium trilaterale, Saccharomyces cerevisiae, and by the mycotoxins, aflatoxin, ochratoxin, oosporein, oxalic acid. Gout and/or hyperuricemia have been induced in humans by the yeast Candida utilis and by the fungal metabolites cyclosporin, ergotamine and penicillin. Gout is documented to be etiologically linked to beer, a Saccharomyces fermented beverage. Beers contain significant amounts of ochratoxin and large amounts (7 to 9 mg/dl of uric acid, a metabolite produced by the brewers's yeast Saccharomyces cerevisiae. Consistent with the fungal etiology of gout and hyperuricemia, the mode of action of colchicine in the treatment of gout is antifungal. Colchicine shares antitubulin activity with griseofulvin, a potent antifungal antibiotic. Griseofulvin is as equally effective in the treatment of gout as colchicine. Similarly, another antitubulin drug, vinblastine is also antifungal and effective in the treatment of gout. All of the other drugs used to treat gout and/or hyperuricemia possess antifungal activity (Costantini 1989).

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- Ustilago Maydis/Moldy Corn-Induced Gout. Jarmai (1925) (2) reported a goose which developed gout after eating moldy corn. Hutyra et al (1926) (3) noted that gout in birds was caused by the smut fungus Ustilago maydis, a common cause of moldy corn. U. maydis, as well as a number of other fungi in the food chain, produces the mycotoxin oosporein.

Oosporein Induced Gout in Chickens And Tur-
reported to induce gout in chickens by von Kossa (1899) (12). It is important to note that uric acid degrades to oxalic acid, a finding described by Wells (1914) (13). This explains why both oxalate and urate are both usually present in kidney stones which occur in gouty patients.

**Yeast Autolysate-Induced Hyperuricemia in Rats.** Long-term feeding of rats with yeast autolysate has caused hyperuricemia associated with a rise in the level of anti-DNA antibodies (Nikolenko et al 1989) (14). These findings appeared to correlate with the finding of significantly elevated titres of anti-DNA in 70 of patients with primary gout. The elevated anti-DNA titres correlated with the severity of gouty arthritis and the severity of morphological renal manifestations of gout. The anti-DNA findings also correlated with blood B-lymphocyte counts and with other immunological indices.

**Yeast (Saccharomyces Fermented Beer and Wine)-Induced Gout In Humans.** Beer and or wine are the classical inducers of attacks of acute gout in humans. Ultraviolett microscopy has demonstrated uric acid, purines, lysine and S-adenosylmethionine in the vacules of S. cerevisiae (Svihla et al 1963) (15). Beer and wine are fermentations of Saccharomyces cerevisiae. Actually, drinking beer and wine is quite the same as drinking a fungal culture; all of the media, all if the remaining live fungus, all of the fungal antigenic cell wall and cellular contents, and all of its metabolites including not only the alcohol, but generous amounts of mycotoxins and uric acid.

While all contemporary studies have attempted to implicate the alcohol in fermented beverages as the cause of hyperuricemia, the older literature contains references to the yeast cell content of beer. Ingestion of beer whose alcohol content had been completely removed by distillation was still associated with large amounts of purine bodies being found in the urine (Lindsay 1913) (16).

Preformed uric acid is present in large amounts in beer. The actual amounts of uric acid found in beer are summarized in Table I.

Moreover, alcohol itself is immunotoxic, which increases the incidence of infections in general. The combination of immunotoxic alcohol and mycotoxins in beer and wine probably represents synergism of a fungal/mycotoxin etiology of gout and hyperuricemia. Large amounts of ochratoxin, which causes gout and hyperuricemia in animals, has been found in beer by Krough et al (1974), Chu et al (1975), and Nipet al (1975) (17,18,19). Gibson et al. found in a group of 61 gouty men, that nearly all were found to be beer drinkers with 41% drinking more than 2.5 liters of beer daily.

**Table I. Uric Acid Content of Various Beers**

<table>
<thead>
<tr>
<th>Brand of Beer</th>
<th>Uric Acid (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miller Beer</td>
<td>7.34</td>
</tr>
<tr>
<td>Olympia Beer</td>
<td>7.05</td>
</tr>
<tr>
<td>Budweiser Beer</td>
<td>8.09</td>
</tr>
<tr>
<td>Taiwan Beer</td>
<td>9.35</td>
</tr>
</tbody>
</table>

**Candida Utilis Induced Hyperuricemia In Humans** Edozien et al (1970) (20) documented that feeding C. utilis to human subjects caused severe hyperuricemia. Their results are summarized in Table II.

**Table II. Hyperuricemic Effects of Uric Acid Containing Yeast**

<table>
<thead>
<tr>
<th>Serum Uric Acid (mg%)</th>
<th>Baseline Before Yeast Feeding</th>
<th>45g Yeast per day</th>
<th>90g Yeast per day</th>
<th>135g Yeast per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.5</td>
<td>7.2</td>
<td>9.0</td>
<td>9.6</td>
<td></td>
</tr>
</tbody>
</table>

Cytotoxic agents, particularly against cells of the immune system. All cytotoxic agents possess antifungal activity. Cyclosporin has been documented to possess selective antifungal activity against Cryptococcus (Mody et al 1989) (26). The remote possibility that the antifungal effect was in any way related to the immunosuppressant effects of Cyclosporin was essentially ruled out by their observation that the improved survival was noted in both immunologically intact and congenitally T-cell deficient mice. Cyclosporin dramatically increases the risk of infection in general and of fungi other than Cryptococcus. This appears to be similar to the phenomena seen with therapeutic use of penicillin causing an overgrowth of other microbes including yeast infections.
Previously Postulated Mode of Action of Colchicine

The actual mechanism of action of colchicine in the treatment of gout has remained unknown. This state of events is most certainly not due to a paucity of studies either in clinical medicine nor in the basic biological sciences. Colchicine has captured the attention of a broad array of scientists around the world and over a quite long period of time. Its dramatic and easily visualized effect on the cellular spindle has been the subject of considerable investigation. Yet, despite all of this attention, the mechanism of its dramatic action in treating an acute attack of gout has continued to remain one of the great mysteries of medical science.

The presently held theory of the mechanism of action of colchicine in gout is one of cytotoxic immunosuppression resulting in an antiinflammatory effect. This concept is based upon in vitro studies of the effect of toxic doses of colchicine upon white blood cells and these types of toxicological studies have resulted in the following scenario:

Colchicine arrests cell mitosis in the metaphase, due to failure of spindle formation, and may prevent cells from entering mitosis. Colchicine has the same effects on the leukocytes incapable of responding to the toxicity of urate crystals. It is this interference with the immune system responsiveness of the acute gouty granulomatous-type inflammatory reaction which gives the patient relief of his inflammation.

The scenario is supported by data such as colchicine inhibits leukocyte adhesiveness (Malawista 1965) (28) amoeboid motility (Malawista 1965) (29), mobilization (Fruhman 1960) (30), chemotaxis (Phelps 1970) (31), degranulation of lysosomes (Rajan 1966) (32), and leukocyte metabolism during phagocytosis (Goldfinger 1965, Wechsler et al 1965) (33, 34). The most potent inhibitory effects of colchicine are on chemotaxis (Phelps 1970) (35) and random motility of leukocytes under the influence of urate (Phelps 1969) (36). However, in order to produce any of these findings, it is necessary to give, per unit mass of experimental material, up to approximately 100 times the therapeutic dose which is effective in gouty patients (Talbott 1965).

Several clinical studies have documented that the leukocytes are not actually affected by colchicine administered to patients in therapeutic levels. Colchicine in clinically effective doses produced no detectable ultrastructural changes in the leukocytes in synovial biopsies of patients with acute gouty arthritis (Agudelo and Schumacher 1973) (37). In patients treated with 0.6 to 1.8 mg per day of colchicine to prevent recurrences of familial Mediterranean fever, neutrophils were capable of normal phagocytosis, produced normal amounts of pyrogen, and migrated normally, both randomly and in response to chemotactic stimuli (Dimarello et al 1976) (38). Furthermore, colchicine failed to influence the behavioural responses to the irritating effects of urate crystals in urate arthritis induced by injecting urates into the ankle joint of rats (Codere and Wall 1988) (39).

Obviously, the postulate that colchicine is antiinflammatory by restricting the function of neutrophils has been essentially disproved in both animals and in humans.

Antigout and Antifungal Activity of Colchicine

Antigout Effectiveness of Colchicine. Colchicine is a plant alkaloid whose benefit in the treatment of gout is recorded in the most ancient medical records. Early descriptions of its use leave little doubt of its effectiveness: "In the first trial of the medicine, it (colchicine) proves in most instances a powerful palliative or..."
short cure; removing the paroxysm as by a charm, and not infrequently without any very sensible operation upon the stomach, or upon any of the excreting organs”.

Scudmore (1817) (40)

Colchicine has always been, and still is, the most specific treatment for acute gouty attacks (Ahern et al 1987) (Famaey 1988) (41) (42). Even the administration of anti-urate drugs often requires the addition of colchicine to control continuing acute attacks of gout.

**Antifungal Activity of Colchicine.** Colchicine is a plant-derived alkaloid. Such alkaloids are anti-predator and antifungal in their actions as plant protectors. (Mothes et al 1988) (43).

The antifungal activity of Colchicine against Aspergillus niger was documented by Shankhla and Sharma (1969) (44). Other reported data demonstrating the antifungal activity of colchicine was reviewed by Egisti and Dustin (1955) (45). This data is summarized in Table III.

<table>
<thead>
<tr>
<th>Species</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allomyces javanicus</td>
<td>changes were induced</td>
</tr>
<tr>
<td>Aspergillus spp.</td>
<td>mutants were produced</td>
</tr>
<tr>
<td>Betylris cincerea</td>
<td>hyphae became hypertrophied</td>
</tr>
<tr>
<td>Caprinus radians</td>
<td>condida influenced</td>
</tr>
<tr>
<td>Diaparthe perniossa</td>
<td>prevented condida formation</td>
</tr>
<tr>
<td>Mucor sp.</td>
<td>no changes noted</td>
</tr>
<tr>
<td>Penicillium notiatum</td>
<td>polykoids</td>
</tr>
<tr>
<td>Paehocyte sernilanceolata</td>
<td>condida changed</td>
</tr>
<tr>
<td>Saccharomyces cervesae</td>
<td>cytological changes, cells enlarged, dumbbell-shaped nuclei, inhibition of growth</td>
</tr>
</tbody>
</table>

**TABLE III. ACTION OF COLCHICINE ON FUNGI**

Species | Results
--- | ---
| Allomyces javanicus | changes were induced
| Aspergillus spp. | mutants were produced
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| Caprinus radians | condida influenced
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| Mucor sp. | no changes noted
| Penicillium notiatum | polykoids
| Paehocyte sernilanceolata | condida changed
| Saccharomyces cervesae | cytological changes, cells enlarged, dumbbell-shaped nuclei, inhibition of growth

Recently, in a murine Candida study comparing the results of intravenous phorbol myristate acetate and intraperitonal colchicine, both drugs completely eliminated the epidermal neutrophilic infiltrates characteristic of these infections (Sohnle and Hahn 1989) (46). The resultant degree of Candida invasion into the dermis was very significant in the phorbol myristate acetate treated animals but quite minimal in the colchicine treated animals. The results are quite indicative of the in vivo antifungal protective effect of colchicine.

The fact that colchicine is an antitubulin drug which shares this mode of action with the antifungal antibiotic griseofulvin has been entirely ignored in the clinical applications of colchicine.

We have here a situation where the major mode of action of these two drugs, sharing no other apparent action, has been entirely ignored in understanding the clinical effectiveness of one of the drugs, colchicine. The extent of this error of perception becomes quite apparent in the light of the observation that griseofulvin, a specific antifungal antibiotic possessing no other significant pharmacological property, is equally as effective as colchicine in relieving an acute attack of gout.

**ANTIGOUT AND AHTIFUGAL ACTIVITY OF GRISEOFULVIN**

- **Antigout Effectiveness of Griseofulvin.** There are two reports in the medical literature of dramatic responses of acute gout to the specific antifungal agent griseofulvin. Both reports appeared in 1962 and there have been no additional followup studies reported since that time.

The rational for these trials was that gouty patients given griseofulvin for superficial fungal infections observed that their painful joints had also markedly improved.

In the first study, the use of moderate to high doses of griseofulvin to treat acute gouty arthritis resulted in complete remissions in 14, partial remission in 2, out of 23 patients within 24 to 48 hours (Slonim et al 1962) (47). There were 23 patients with acute gouty arthritis in the series. Included were histologic proof of tophi in 15 patients; dramatic clinical improvement in 22 patients during colchicine trial administered by standard technic for a previous acute attack in 12; two or more serum uric acid levels greater than 6.5 mg, per cent in 22 cases; and x-ray evidence of bone destruction in 17 of the group. Side effects were negligible but 6 out of the 7 patients who did not improve suffered vomiting episodes during the period of drug dosing and were felt to not have retained therapeutic amount of the drug. 1.0 to 4.0 g. of griseofulvin was given orally at the onset of the study to the gouty patients, with further dosage at 6 hours spacings. Eighteen of these patients received 4 to 10 g total dosage during the first day and 0 to 6 g on the second. Higher doses were prescribed for 5 patients to demonstrate, if possible, an effect on serum and urine uric acid concentrations; none was seen.

In the second report, 20 patients with acute gout were treated and favorable improvement was noted in 15 (Wallace and Nissen 1962) (48). Once again, the optimal response occurred within 24 to 48 hours. Patients were given 6-10 g of griseofulvin in divided doses.

**Antifungal Activity of Griseofulvin.** Griseofulvin is a specific antifungal antibiotic. It was first isolated from Penicillium griseofulvium dierckx in 1939 (Oxford et al) (49), but it was not investigated further at that time because it lacked antibacterial activity. In 1946 Brian et al (50) found a metabolite in Penicilium janczewskii which caused shrinking and stunting of fungal hyphae. They named this "curling factor" which was subsequently found to be griseofulvin. During the next decade, it was widely used to treat a variety of fungal diseases of plants and ringworm of cattle. Its potential for the treatment of human infections was not realized until Gentles (1958) (51), searching for potential therapeutic agent to control fungal infections in Scottish miners, demonstrated that oral griseofulvin was effective in experimental Microsporum canis infection of guinea pigs. It was soon shown that the drug was also effective in human ringworm infections.
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(Williams et al 1958, Blank et al 1959) (52,53). Griseofulvin is now generally accepted as the drug of choice for treatment in the majority of these fungal diseases.

AHFICOST AND ANTIFUNGAL ACTIVITY OF VINBLASTINE

• Antigout Effectiveness of Vinblastine. Another member of the antimicrotubule group of agents effective in treating gout is vinblastine. It has been demonstrated to be as effective as colchicine in the treatment of acute gout (Krakoff 1965) (54).

Antifungal Activity of Vinblastine. In 1983, the similarity of actions of vinblastine, griseofulvin and colchicine was demonstrated in a unicellular alga. Electron microscopy demonstrated conspicuous morphological abnormalities resulting from inhibition of microtubule dependent protoplasmic streaming (Mizukami and Wada 1983) (55). The authors noted that very similar changes had been previously reported in Fusarium acuminatum treated with another antimicrotubule agent, methyl benzimidazole-2-ylcarbamate.

It should be noted that the latter compound is an azole and that the azoles are evolving as a most promising group of antifungal agents with several members of the group in current use (ketocanazole, fluconazole, etc.) and a number of others are near-ready for marketing.

CONCLUSION

• The unified concept of a fungal etiology and an antifungal mode of action of antigout drugs provides a clinically meaningful therapeutic drug and dietary approach not only for the physician, but, most importantly, for the patient afflicted with gout, particularly those who are been drinkers and are consuming other yeast-fermented beverages and foods such as wine, bread and cheese.

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