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RECENT DEVELOPMENTS IN THE THERAPY OF CHROMOBLASTOMYCOSIS[1]

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Treatment of chromoblastomycosis patients with a combination of 5-fluorocytosine and amphotericin B has yielded encouraging results. Even though the dosage of both drugs was considerably lower than the standard dosage for chromoblastomycosis of either used alone, treatment appeared successful and no cases of resistance to 5-fluorocytosine occurred.

There was no specific treatment for chromoblastomycosis until 5-fluorocytosine became available. A number of different drugs and therapeutic procedures were used for this mycosis, but none had proved absolutely effective.

The first cases of successful treatment of chromoblastomycosis using 5-fluorocytosine, substantiated by monitored results, were reported by Lopes and colleagues *(10, 11, 12, 13, 15)*.

Flucytosine (5-fluorocytosine, or 5-FC) is a fluorinated pyrimidine that actively combats the following fungi: *Candida albicans, Cryptococcus neoformans,* and the agents causing chromoblastomycosis. The way it acts on these fungi is not yet clearly understood. Contact with the fungus produces deamination of the drug, and its deaminated form—known as 5-fluorouracil—apparently inhibits protein synthesis in the parasite *(21-24)*.

Cryptococcosis, systemic candidiasis, and chromoblastomycosis have been successfully treated with 5-FC. It is produced in the form of 500-mg tablets for oral administration, and the recommended dosage ranges from 100 to 200 mg/kg of body weight daily, divided into 4 doses. Over 98 per cent of the drug is excreted virtually intact in the urine; thus it is not metabolized or retained by the body *(24)*. Perfect renal function is therefore required. In the event of any change, the patient should be tested for creatinine clearance to determine the proper dosage. It can be administered on a long-term basis *(10, 11, 12, 13, 15)*. Certain authors cite the occurrence of leukopenia in cases where daily doses exceed 100 mg/kg/day *(27)*, but we have used 200 mg/kg/day in a number of patients without encountering this problem *(10, 11, 12, 13, 15)*.

With the help of our colleagues, we tested the use of 5-FC in treating 23 chromoblastomycosis patients, closely monitoring the results: 16 were actually cured (Figure 1) and 7 developed a resistance to 5-FC (Figure 2) but showed improvement *(16)*.

With the use of 5-FC, patients can be cured in 2 months to 1 year, depending on the individual case. Those with small, isolated lesions and a short history of infection respond to the treatment more quickly. Those with widespread lesions and/or a long-standing history of infection take 8 months to a year or more to respond, and eventually tend to develop a resistance to 5-FC. It should be noted that, in dealing with chromoblastomycosis, short term means 1, 2, or up to 3 years, and even such instances can be described as recent.

Resistance to 5-FC

Resistance to 5-FC had already been noted in connection with systemic candidiasis and cryptococcosis, but we were the first to report its development in chromoblastomycosis cases *(16)*. It occurs when treatment is prolonged:

[1] From *Superficial, Cutaneous, and Subcutaneous Infections: V International Conference on the Mycoses,* PAHO Scientific Publication 396, Pan American Health Organization, Washington, D.C., 1981, pp. 344-349.

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following appreciable improvement, the patient reaches a plateau or deteriorates. Isolates tested *in vitro* for sensitivity to the drug showed resistance to over 10 μg/ml. Cultures were made to test each patient's sensitivity to the drug before starting treatment in every case. We observed that resistance developed in patients with widespread lesions and/or a long-standing history of infection (the most recent was 8 years, whereas the most persistent case had lasted 25 years).

We tried unsuccessfully to overcome this resistance by combining 5-FC with other drugs used to treat chromoblastomycosis, such as calciferol, thiabendazole, and amphotericin B. We found, however, that once entrenched, the resistance could not be eliminated *(16)*. The same findings had already been noted in connection with candidiasis and cryptococcosis (1, 2).

The mechanism that causes resistance to develop is not yet known. Miyamoto and col-

Figure 1. Cases of successful treatment of chromoblastomycosis with 5-fluorocytosine.

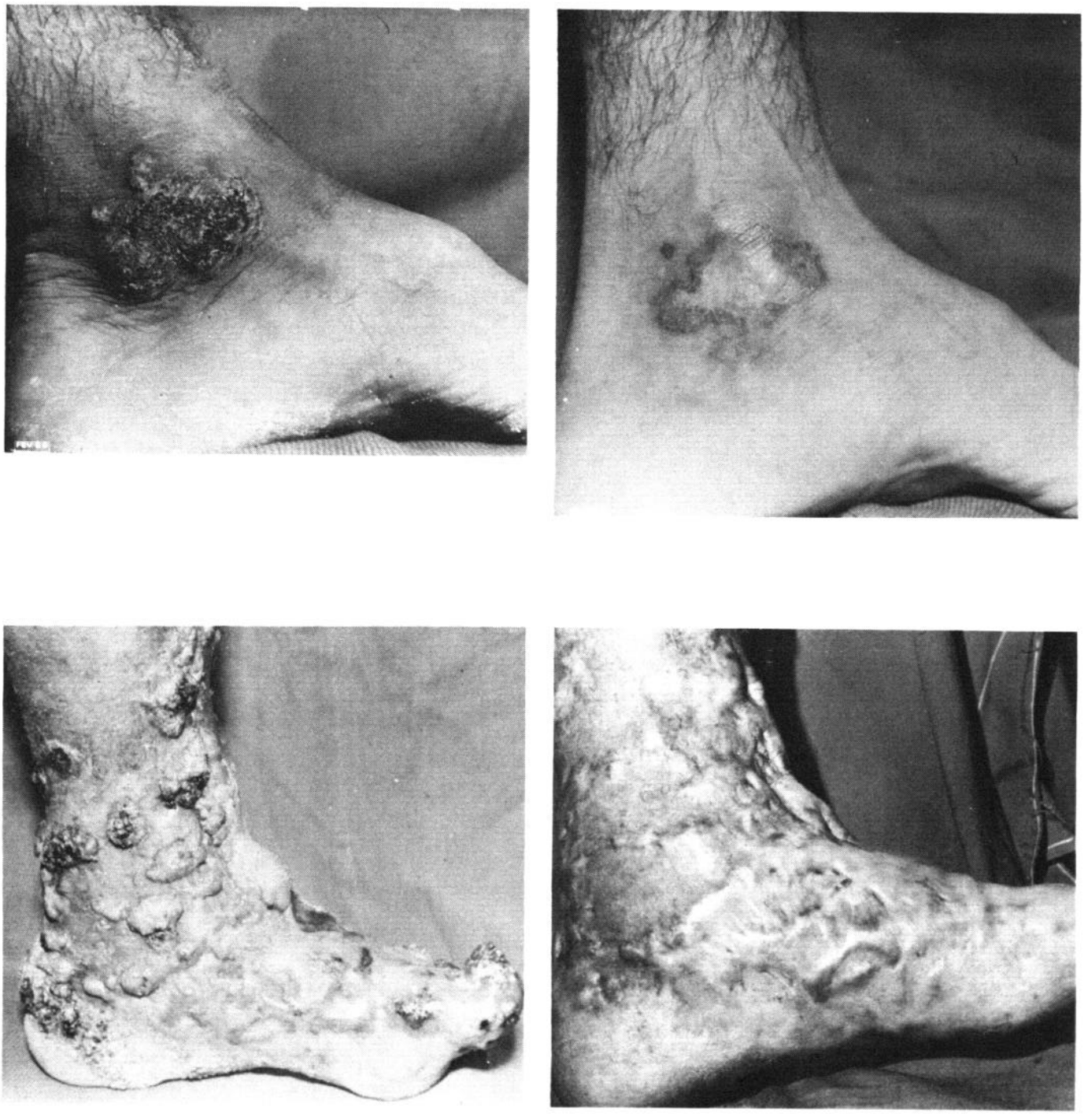
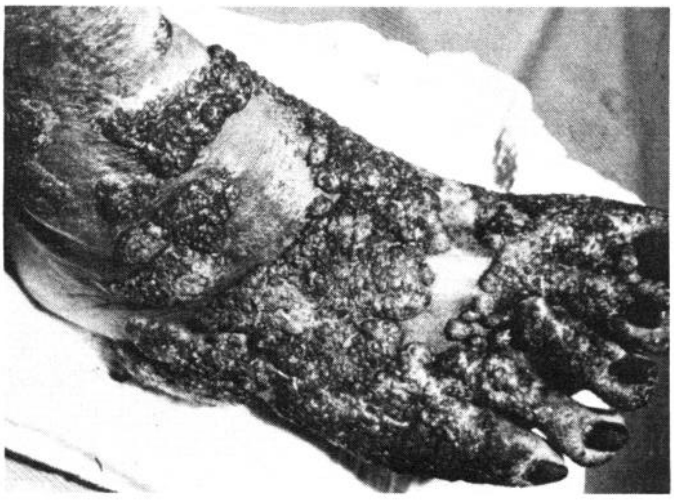
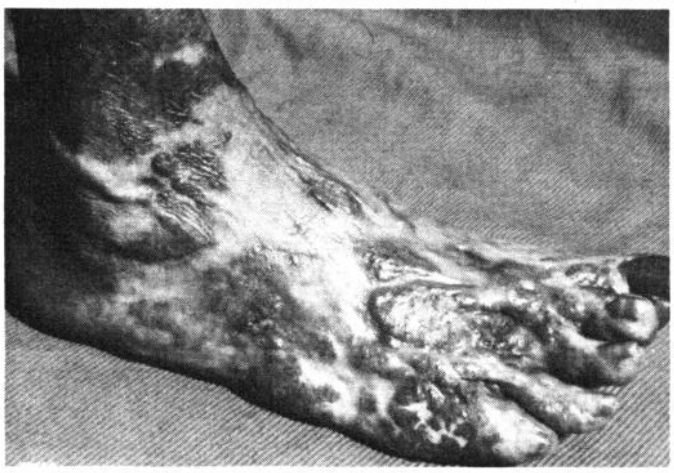


Figure 2. Cases of resistance to 5-fluorocytosine after improvement was obtained.





leagues *(18)* attribute it to the lack of deaminated cytosine following UMP (uridine-monophosphate-pyrophosphorylase) which blocks deamination. The failure of the fungus' RNA to absorb the deaminated form—5-fluorouracil—prevents the fungus from responding to the drug.

Association of 5-FC and Amphotericin B

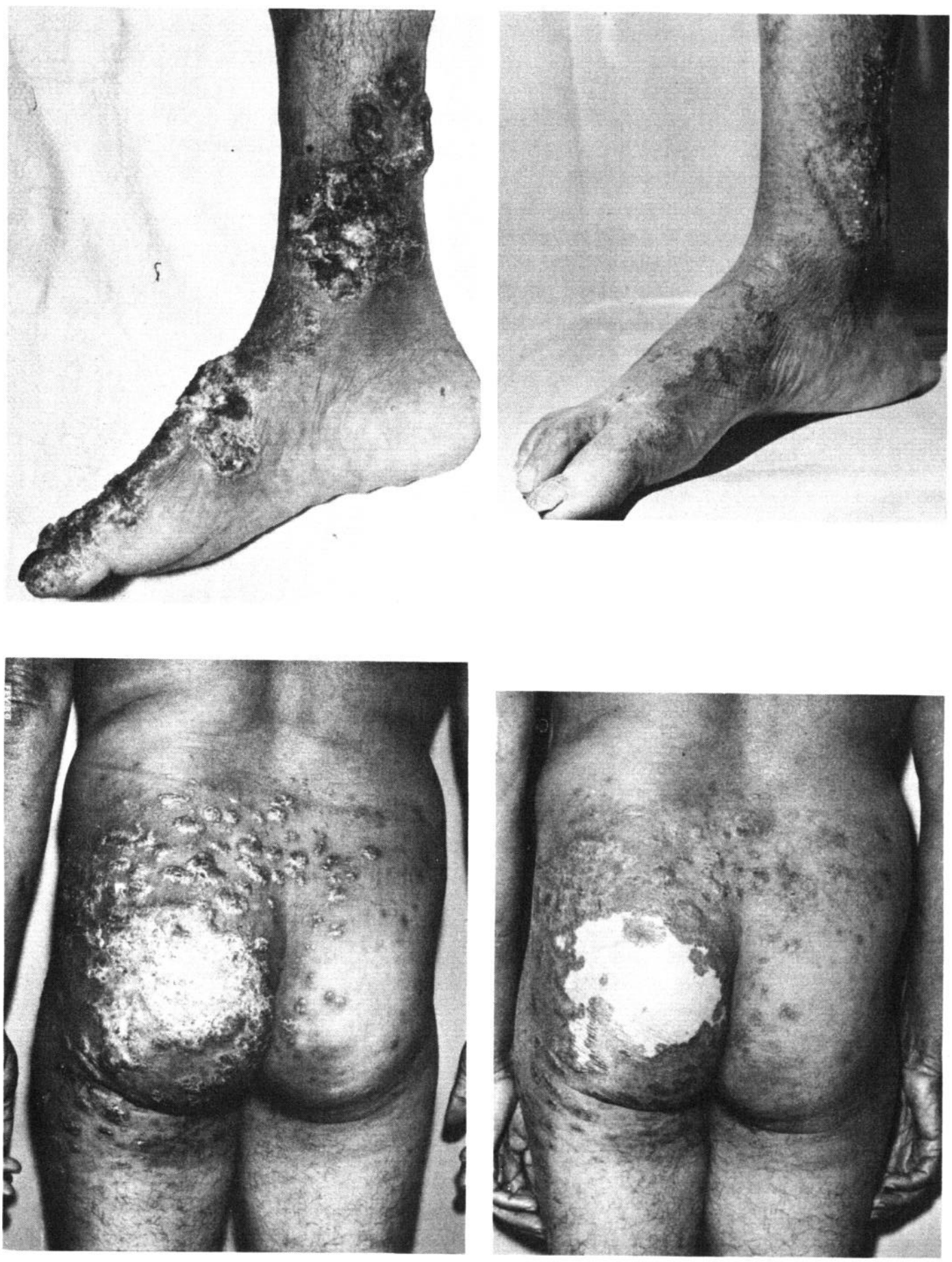
Unable to overcome resistance to 5-FC because of increasingly opportunistic fungi in two serious infections, systemic candidiasis and cryptococcosis, researchers started with the premise that the most effective drugs for these two diseases were amphotericin B and 5-FC. When administered in the high dosage needed for treatment, the first is highly toxic and cannot be tolerated by the patient; and the second, though signally efficacious and well tolerated, triggers the development of resistance. The researchers therefore decided to use the two drugs in combination in the hope of eliciting a simple complementary—or, if possible, synergetic—action such as had been obtained in treating tuberculosis. Fortunately, tests *in vitro* and *in vivo* in mice with *C. albicans* and *C. neoformans* fungi disclosed a synergetic action between the two drugs *(1, 3, 17, 21, 22, 26)*. It might be added that Resende and colleagues *(23)* observed the same synergism *in vitro* with isolates of *Fonsecaea pedrosoi* taken from our patients.

The synergetic action of the two drugs is explained by the fact that amphotericin B is a polyene antibiotic and as such acts on the cytoplasmic membrane of the fungus, making it more easily penetrated by 5-FC, which therefore has a stronger effect on the parasite, inhibiting protein synthesis *(3, 20, 22, 26)*. In addition, amphotericin B prevents resistance to 5-FC from developing *(1, 20, 25, 26)*. The laboratory findings were then taken to the clinical level, where treatment of systemic candidiasis and cryptococcosis with the combination of 5-FC and amphotericin B proved successful *(6, 7, 8, 9, 19, 27)*.

The use of this combination to treat chromoblastomycosis was a logical next step since these three mycoses represent the specific action spectrum of 5-FC and, by extension, of amphotericin B. Accordingly, this does not constitute the discovery of a new method of treatment *(4, 5)*.

We too used this combination of drugs to treat chromoblastomycosis (Figure 3), with excellent results *(14)*. We treated five male patients over 36 years of age who had had the disease for periods ranging from 6 to 19 years. Three of them had widespread lesions. We took advantage of the synergetic action of the combination to reduce the dose of each significantly, using 75 mg/kg/day instead of the recommended 100-200 mg/kg/day of 5-FC and only 25 mg of amphotericin B every other

Figure 3. Cases cured with the combination of 5-fluorocytosine and amphotericin B.



day—equivalent to approximately 0.20 mg/kg/day—instead of the recommended 1 mg/kg/day, which few patients can tolerate.

Treatment was discontinued in one case, following substantial improvement. The other four patients were discharged with negative histopathologic and mycologic test results and there were no signs of recurrence 2 to 3 years later.

We are now continuing our observations with a second group of patients as a basis for another published work. For this group, we cut the dose of 5-FC still further to 50 mg/kg/day, while continuing amphotericin B every other day. Seven male patients were treated; they ranged from 39 to 74 years of age. Except for 1 with a 7-month history of infection, they had suffered from chromoblastomycosis for 5 to 20 years. Four had extensive lesions.

The reduced dosage given this second group did not impair the efficacy of the treatment, which was completely satisfactory: two of the patients were discharged after histopathologic and mycologic tests proved negative. Here, too, there was no recurrence within 12 to 18 months.

We have observed that the combination of 5-FC and amphotericin B acts faster than does 5-FC alone and that, in follow-up testing during treatment, negative histopathologic and mycologic results are achieved sooner.

On the other hand, we must emphasize the predominance of long-standing infection and widespread lesions in the two groups observed, which would undoubtedly have resulted in the development of resistance to 5-FC in several, if not all, patients had treatment consisted exclusively of that drug. The fact that not a single case of resistance occurred is due to the combination with amphotericin B.

The small doses of 5-FC and amphotericin B that we used offer a number of advantages. The risk of side effects from 5-FC is reduced *(2)*. Given the high price of 5-FC, the treatment costs less. The renal toxicity of amphotericin B is minimized, and it is better tolerated by the patient.

Finally, the fact that we were able to observe the treatment of 23 patients with 5-FC alone over a period of 6 years *(15)* and that we have now been using 5-FC and amphotericin B in combination for almost the same length of time allows us to compare the results obtained and to submit the following conclusions:

1) 5-FC is the most effective drug to combat chromoblastomycosis, but it elicits resistance;

2) the combination of 5-FC and amphotericin B also cures this mycosis;

3) both 5-FC alone and the combination of 5-FC and amphotericin B are well tolerated and have no undesirable side effects;

4) the combination of 5-FC and amphotericin B prevents the development of resistance to 5-FC;

5) even mild cases of recent origin and/or with small or isolated lesions should be treated with a combination of 5-FC and amphotericin B rather than 5-FC alone, because resistance to 5-FC cannot be overcome once it develops;

6) the combination is more effective and monitoring shows that negative results are achieved earlier in histopathologic and mycologic tests;

7) the synergism of the combination of 5-FC and amphotericin B makes it possible to use smaller doses effectively in treating this mycosis, thus confirming laboratory findings;

8) the use of smaller doses has a number of advantages:

a) it reduces the possibility of side effects from 5-FC and lowers the cost of treatment with this drug;

b) it minimizes the renal toxicity of amphotericin B, making it more easily tolerated; and

9) finally, although the number of cases treated is still relatively small, there appears to be no doubt that the combination of 5-FC and amphotericin B is the treatment of choice for chromoblastomycosis.

SUMMARY

There was no specific treatment for chromoblastomycosis until 5-fluorocytosine became available; and although this drug has proved successful in curing many cases, resistance has been noted—especially among patients with widespread lesions or a long history of infection. Such resistance typically develops when treatment is prolonged, following appreciable improvement.

To help deal with this problem, amphotericin B and 5-fluorocytosine (a combination that has been used successfully to treat systemic candidiasis and cryptococcosis) was administered to five chromoblastomycosis patients, three of whom had widespread lesions. Because of the two drugs' synergistic action, the normal dosage of each could be reduced—to 75 mg/kg/day of 5-fluorocytosine and 25 mg of amphotericin B every other day.

Treatment of one case was discontinued after substantial improvement. The other four patients were discharged with negative histopathologic and mycologic findings. Similar treatment of seven other chromoblastomycosis patients, with the 5-fluorocytosine dosage reduced to 50 mg/kg/day, did not impair the efficacy of treatment, and no cases of resistance to 5-fluorocytosine emerged.

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LOW BIRTH-WEIGHT REVIEWED

A recent review published in WHO's *World Health Statistics Quarterly Report*[1] provides a comprehensive overview of the low birth-weight problem around the world. The review, based on information derived from 280 previous studies in 90 countries, points out that birth weight is, "in all population groups, the single most important determinant of the chances of the newborn to survive."

In all, the report estimates, some 21 million infants born in 1979 were of "low birth-weight," weighing 2,500 grams or less. This figure represents 17 per cent of all the live births (about 122 million) in 1979. The low birth-weight problem affected some areas far more seriously than others, however, nearly 50 per cent of the newborns in some parts of Asis having low birth-weights, while in some parts of Europe the proportion involved was only 6 per cent. Overall, the estimated numbers of infants with low birth-weight in major geographic regions were as follows: North America, 296,000 (7 per cent of all live births); Europe, 536,000 (8 per cent); Soviet Union, 380,000 (8 per cent); Latin America, 1,400,000 (11 per cent); Oceania, 62,000 (12 per cent); Africa, 3,200,000 (15 per cent); and Asia, 15,000,000 (20 per cent).

In Latin America the highest incidences of low birth-weight were found in Middle America and the Caribbean. The seven countries of Middle America, taken together, had an incidence of 15 per cent (566,000 out of 3.6 million live births), while the six Caribbean nations and Puerto Rico had an incidence of 13 per cent (117,000 out of 870,000 live births).

[1]The incidence of low birth weight: A critical review of available information, *World Health Statistics Quarterly Report* 33(3), 1980.