

THE MODERN TREATMENT OF NORTH AMERICAN BLASTOMYCOSIS*

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THE AROMATIC DIAMIDINES are widely and successfully used in the treatment of trypanosomiasis, leishmaniasis and multiple myeloma.

In 1945, Elson¹ demonstrated the fungistatic action of propamidine against *Blastomyces dermatitidis* "in vitro". Five years later, in 1950, Colbert, Strauss and Green² reported a case of cutaneous blastomycosis treated with propamidine. In 1951, Schoenbach and his associates³ successfully used stilbamidine, another member of the aromatic diamidine group, in the treatment of two patients suffering from systemic blastomycosis. These first papers have been followed by others⁴⁻⁹ which have demonstrated the efficiency of stilbamidine against systemic blastomycosis. However, a persistent trigeminal neuropathy was very frequently a late complication of the use of stilbamidine.

2-Hydroxystilbamidine,† another member of the aromatic diamidine group, was found to have a fungistatic action (*in vitro*) equal to that of stilbamidine, but without any toxic effect on the fifth nerve. Snapper and McVay¹⁰ reported three cases of blastomycosis (two systemic and one cutaneous) in which 2-hydroxystilbamidine produced an arrest of the disease. Colsky,¹¹ Weinberg and his co-workers,¹² Acree and his associates,¹³ London¹⁴ and Macauley¹⁵ have used 2-hydroxystilbamidine in eight cases, with good results. Of these eight patients, five suffered from systemic blastomycosis and three from the cutaneous type. No trigeminal neuropathy was observed. Sutliff, Kyle and Hobson¹⁶ have treated 12 cases of blastomycosis with 2-hydroxystilbamidine, with arrest of the disease in seven, improvement in two, and no effect in three cases. The treatment failures were found in patients suffering from advanced pulmonary blastomycosis. In none of these 12 cases did 2-hydroxystilbamidine produce a toxic effect on the fifth nerve. Doray and his associates¹⁷ and our own preliminary report¹⁸ on two cases of systemic blastomycosis treated with this drug have shown its efficiency and its absence of nervous complication.

The few treatment failures or relapses seen in the treatment of this disease with 2-hydroxystilbamidine were observed¹⁹⁻²⁰ in patients having a negative skin test to blastomycin and a positive complement-fixation test. Harrell and Curtis²¹ successfully used another drug, amphotericin B, in

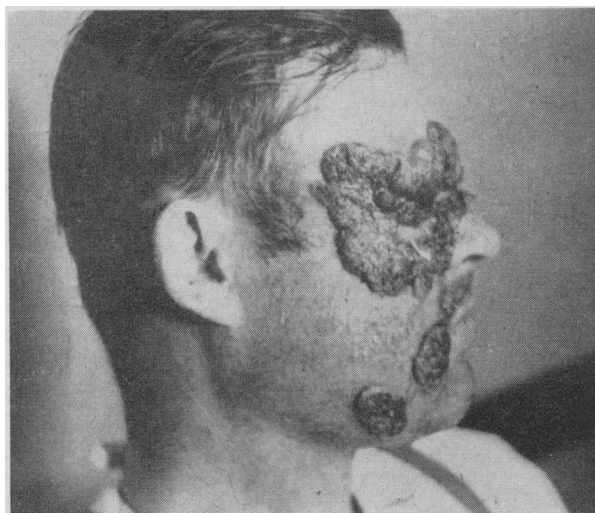


Fig. 1

these resistant or relapsing cases. This new drug has a promising future²² in spite of the febrile and digestive complications to which it gives rise.

CASE REPORTS

This paper will report three cases of systemic blastomycosis, one treated with stilbamidine and 2-hydroxystilbamidine, with three years' follow-up, and two treated solely with 2-hydroxystilbamidine.

CASE 1.—R.B., a 35-year-old farmer, was admitted to St. Sacrement Hospital on November 13, 1946, because of granulomatous patches of a few months' duration on the face (Fig. 1), the right hand and the soft palate. A tentative clinical diagnosis of blastomycosis was supported by a histopathological examination and cultures of the lesions. A blastomycin skin test was strongly positive (4 plus). Radiograph of the chest was normal.

After an unsuccessful therapeutic trial of high doses of calciferol (vitamin D₂),²³ the patient was treated with a vaccine, a saturated solution of potassium iodine, and radiotherapy. The lesions healed slowly, but during the treatment an orchio-epididymitis, complicated by a scrotal fistula, occurred. Budding organisms were found in the exudate from the fistula. In July 1947, the patient was discharged from the hospital very much improved.

He was seen again in June 1949, for a recurrence of his orchio-epididymitis with slight discharge from the fistula. No organism was found. Solution of potassium iodine was prescribed.

In March 1955, the patient was readmitted with very pronounced swelling of the scrotum and the penis



Fig. 2

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†2-Hydroxystilbamidine was graciously made available to me by Dr. R. H. McMaster, research associate of the Department of Medical Research, The Wm. S. Merrell Company.

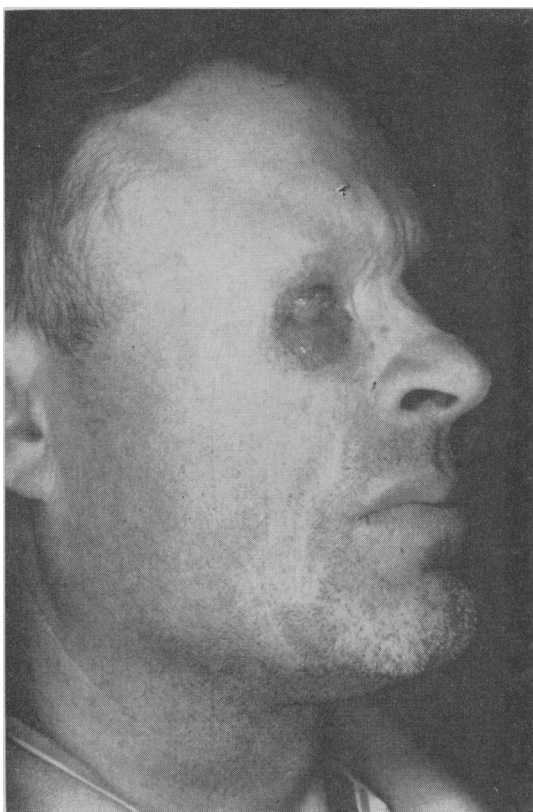


Fig. 3

accompanied by a discharge from a scrotal fistula. Elevated, well-circumscribed granulomatous and verrucous patches were present on the scrotum (Fig. 2) and the upper and inner aspects of the left thigh. The right side of the face was partly covered by a large whitish scar, and the right eye was covered by a whitish membrane and surrounded by a bright red denuded area, slightly oozing and crusted (Fig. 3).

A skin biopsy from the border of the patch of the left thigh showed the following lesions:

Low magnification.—There is a pseudo-epitheliomatous hyperplasia of the epidermis, with minute abscesses. Within these abscesses, some giant cells can be seen.

High magnification.—The central portion shows two blastomycetes surrounded by polymorphonuclear neutrophils. The spores show a thick wall, giving them a double-contoured appearance (Fig. 4).

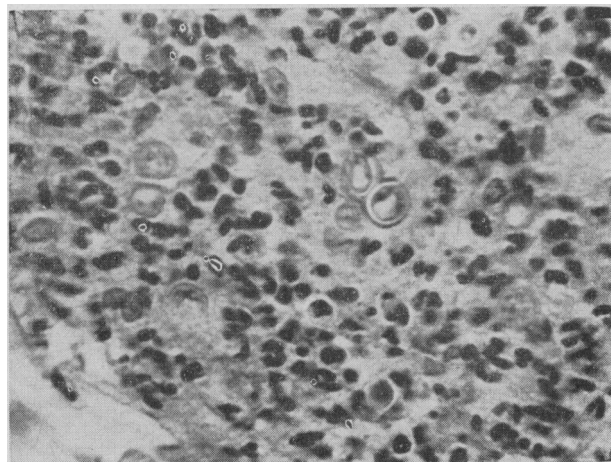


Fig. 4

A culture from the same lesions was positive for *Blastomyces dermatitidis*, and a skin test to blastomycin was strongly positive. On March 12, 1955, a chest radiograph showed the left hilar shadow to be somewhat increased in size; linear strands were seen radiating from the left hilum towards the lung field. At the left base, there was an ill-defined area of increased density, which was in part overshadowed by the apex of the heart. Lung fields were otherwise clear. No organism was found in the sputum.

From March 22 to May 9, the patient received 21 intravenous infusions of 150 mg. of stilbamidine, diluted in 250 c.c. of 5% glucose. A total dosage of 3.15 g. of stilbamidine was given during this period. Three weeks after onset of treatment, improvement was grossly evaluated at 50%. The patches were drier, less elevated and starting to heal in the centre.

Repeated urine examinations, at first normal, revealed albumin in large amounts after 12 days of stilbamidine. The administration of stilbamidine was then reduced to bi-weekly injections and the urine was normal again. Blood counts and liver function remained normal.

On April 19, less than a month after the onset of stilbamidine therapy, the patient complained of slight neuralgia on the right side of his face.

Hydroxystilbamidine therapy was begun on May 9, and he received 5.4 g. of this drug in a 35-day course. During this course, the only toxic symptom was a slight anorexia which lasted a few days, but the trigeminal neuropathy caused by stilbamidine was persistent. Routine laboratory examinations were normal. On June 17, 1955, the patient was discharged. All the active lesions of blastomycosis were completely healed (Fig. 5).

When seen in August 1955, June 1956 and April 1958, the patient presented no recurrence of his deep mycotic infection. Radiographs of the lungs were normal. After a follow-up period of almost three years there was still persistence of a slight trigeminal neuropathy.



Fig. 5

CASE 2.—T.P.E., a 53-year-old farmer, was admitted to Laval Hospital on June 21, 1956, for coughing spells, loss of weight, asthenia and pain in the left chest. These clinical symptoms had appeared about two months previously.

Numerous sputum samples and gastric washings were examined and cultured for tubercle bacilli, but none were found. Radiographs of the chest showed a homogeneous opacity of the left apex (Fig. 6). The sedimentation rate was 64 mm. in one hour. A complete blood count revealed a slight anaemia and a leukocytosis of 11,600 per c.mm.

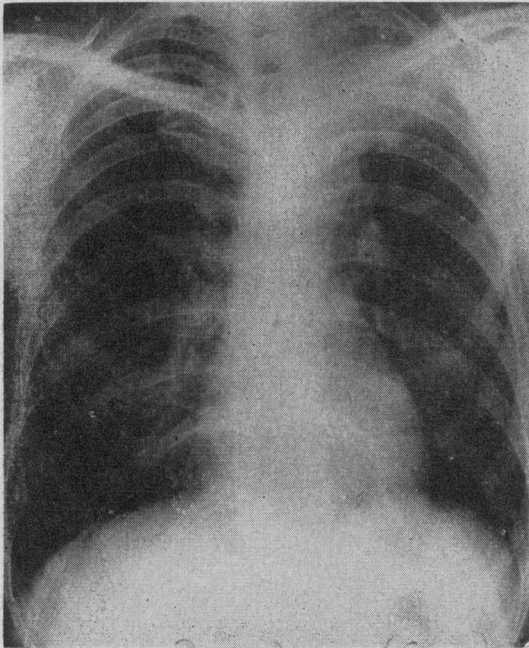


Fig. 6

Three weeks after his admission, a small papulopustular lesion appeared on his left thumb. Topical and general use of antibiotics did not affect this skin lesion. On bronchoscopic examination, tissue taken from the left upper lobe bronchus showed no evidence of a neoplastic process. A left upper lobectomy was performed on August 29, 1956, because the general condition of the patient was gradually deteriorating, and the pulmonary process was spreading somewhat in spite of the use of antibiotics.

Histopathological sections of the lung tissue removed showed the usual infiltration of pulmonary blastomycosis (Fig. 7) with the presence of organisms in the giant cells.

In mid-September 1956, the patient complained of pain in his left hand accompanied by a degree of limitation of movements of the fingers. There was a slight erythematous swelling on the dorsal aspect of the hand, and palpation was painful over the 3rd, 4th and 5th metacarpals. Radiograph of the hand showed pronounced osteolysis of the base of the 4th metacarpal (Fig. 8). This report suggested an osseous localization of the blastomycotic process.

Before treatment was started with 2-hydroxystilbamidine, it was decided to remove the little papular lesion of the left thumb. Histopathological examination of this cutaneous lesion showed a pseudo-epithelio-

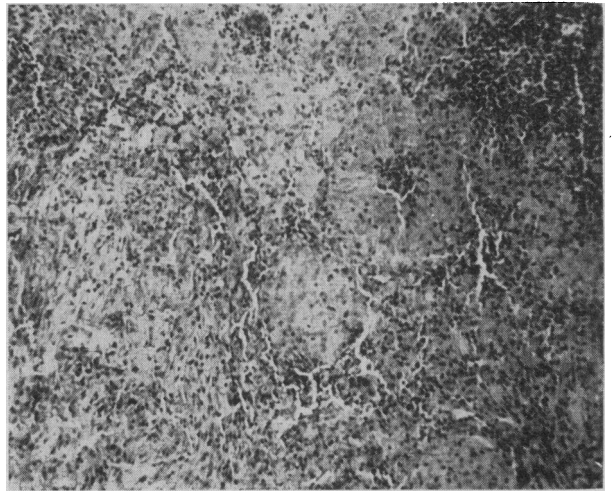


Fig. 7

matous hyperplasia of the epidermis. In the dermis, there were granulomatous formations made up of epithelioid cells, numerous grouped polymorphonuclear cells and some giant cells. A few thick-walled spores were seen.

Beginning on October 20, 1956, 2-hydroxystilbamidine, 225 mg. dissolved in 250 c.c. of 5% glucose solution, was administered intravenously thrice weekly, in a slow drip over two hours. During the first two weeks, the patient suffered from generalized pruritus. At the beginning of December, there was a spontaneous opening of the tumefaction of the left hand, followed by a progressive healing. On February 1, 1957, a small cutaneous scar was the only vestige left (Fig. 9). Radiographs of the chest were normal except for the lobectomy. The patient was feeling well and had gained 10 lb. Blood count was normal, but the sedi-



Fig. 8



Fig. 9



Fig. 10

mentation rate was still 45 mm. On March 13, the sedimentation rate was 27 mm. The left hand showed a non-progressive osteolysis of the base of the 4th metacarpal on radiography. At discharge the patient had received 9 g. of 2-hydroxystilbamidine. A skin test to blastomycin was positive (3 plus). Monthly regular follow-up was irrelevant until December 1957. At this time, the patient complained of moist cough and pain in his left chest. The sedimentation rate and radiographs of the chest were normal, but sputum samples showed some organisms.

Readmitted at the end of January 1958, he again received 9.0 g. of 2-hydroxystilbamidine. Repeated sputum samples did not show any organisms after February 13. The drug was well tolerated. Routine laboratory examinations remained negative throughout this second course. Sedimentation rates varied between 3 and 7 mm. Chest films remained unchanged. A blastomycin skin test was positive (2 plus). When discharged from hospital on May 21, 1958, the patient was presenting no sign of activity of his deep mycotic infection.

CASE 3.—P.R., a 36-year-old construction worker, was admitted to Laval Hospital on January 17, 1957, for slight repeated hæmoptyses, profuse night sweating, and mediastinal and dorsal pains.

Multiple sputum examinations for Koch bacilli and carcinoma cells were negative. The sedimentation rate was 74 mm. in one hour. Other laboratory tests were negative. Radiological examinations of the chest revealed an opacity radiating from the hilum of the left lung to the upper lobe. The right lung was normal.

On February 8, surgical resection of the left lung was carried out, on the assumption that the patient was suffering from a lung carcinoma. The pneumonectomy was done with some difficulty, because the pulmonary lesions were strongly adherent to the thoracic cage and also to the descending aorta. It was impossible to remove completely the diseased tissues in these regions. Frozen sections of the lesions revealed single budding thick-walled spores of *Blastomyces dermatitidis*. Direct examination of the pus (Fig. 10) and cultures of the lung tissue showed the same organisms.

On February 9, 2-hydroxystilbamidine was started. Daily intravenous injection of this drug was given in 250 c.c. of 5% glucose during a two-hour period. In

addition, 125 mg. of 2-hydroxystilbamidine in 100 c.c. of normal saline was introduced into the left pleural cavity on two successive days. By February 20, the patient had received 2.6 g. intravenously and 0.250 mg. in the left thoracic wound.

Hydroxystilbamidine was well tolerated, but unfortunately the treatment was temporarily discontinued because of a shortage in supply. It was resumed on March 6 and continued until March 19. At this last date, the drug was stopped on account of severe toxic symptoms attributed to this treatment. The patient was very tired, anorexic and nauseated. Abdominal and gastric pains were accompanied by bouts of diarrhoea. The skin was dry and slightly scaly, and the pruritus severe. Icterus index was 7.4, and the urine showed 0.25 g. of albumin, free leukocytes and granular casts. Blastomycin skin test was weakly positive.

All these toxic manifestations disappeared rapidly after the discontinuation of hydroxystilbamidine. On March 25, the urine contained only traces of albumin. The sedimentation rate was 15 mm. and the white blood count 4030. Chest films showed a normal right lung. On April 10, the general condition of the patient was good. It was decided to resume hydroxystilbamidine, but at weekly intervals. On July 10, the treatment was stopped. Since the beginning of his illness, the patient had received 9.0 g. by the intravenous route and 0.250 g. in the thoracic cavity. The patient had a good appetite and had gained 10 lb.

His sedimentation rate had returned within the limits of normal, and repeated radiographs of the chest did not show any progress of the disease.

The patient was followed up regularly and it was not until mid-April 1958 that a recurrence was suspected. At that time, he presented with a moist cough, and although his general condition was good and his chest film unchanged, repeated sputum examinations revealed blastomycetes on two occasions.

The use of amphotericin B was considered, but because of the high toxicity of this drug, and the strong positivity (3 plus) of the blastomycin skin test, hydroxystilbamidine was chosen for another trial. The patient was readmitted on May 1, 1958, and hydroxystilbamidine was given thrice weekly in the usual dose of 250 mg.

About one month after his admission (June 4) he had received 3.75 g. without showing any toxic

symptoms. Blood cholesterol was normal, but the icterus index was 9.4. Numerous sputum examinations were negative, except one made on May 26, which was positive.

The treatment is being continued with hydroxystilbamidine. However, we are considering the use of amphotericin B for the next course of treatment if the organism is still present in the near future.

DISCUSSION

The aromatic diamidines, especially 2-hydroxystilbamidine, are very useful drugs in the treatment of systemic blastomycosis. Before 1951, there was no satisfactory treatment for this disease, and the mortality rate was in excess of 90%.

The first case reported here, in which the deep mycotic infection recurred in spite of vaccine, saturated solution of potassium iodide and topical radiotherapy, responded quickly to stilbamidine and 2-hydroxystilbamidine. However, less than a month after the outset of stilbamidine, a persistent trigeminal neuropathy occurred. This very frequent sequel of stilbamidine therapy did not appear in other cases, treated solely with 2-hydroxystilbamidine.

This patient, who suffered from systemic blastomycosis involving the genitalia, the skin and possibly the left lung, shows the efficiency of this group of drugs, since there has been no recurrence in a three-year follow-up.

Cases 2 and 3, both treated solely with 2-hydroxystilbamidine for their systemic blastomycosis, responded well to this therapy without toxic effect on the fifth nerve. Even if these two patients were subjected to extensive surgical procedures, it seems that the drug produced an arrest of the systemic infection. This arrest was temporary, because a few months later they had to be re-treated after positive findings of organisms in the sputum. However, these recurrences were much less severe than the initial infection. Whether the use of larger total doses of 2-hydroxystilbamidine would have prevented these recurrences is a moot question which cannot be answered here.

The toxicity of 2-hydroxystilbamidine has been reported as very low if the solution is made up just before its administration, given by slow intravenous drip and protected from the light. In patients suffering from liver or kidney diseases this drug has to be administered very cautiously.

The second case tolerated the therapy well, and the only toxic symptom was a transient generalized pruritus.

The third case presented severe toxic symptoms which may be explained by previous liver and kidney disease and also by the daily administration of 2-hydroxystilbamidine. These symptoms disappeared after administration of the drug was ceased, and further treatments given bi- or tri-weekly were well tolerated.

The aromatic diamidines are effective in the treatment of North American blastomycosis. Should

this group of drugs fail to attain the desired results, amphotericin B may be used as an alternative.

SUMMARY

Three cases of systemic blastomycosis treated with members of the aromatic diamidine group are reported. All three cases responded to treatment, the follow-up of one case being a period of three years.

The toxicity of these drugs and the possible residual results of treatment are discussed.

I am indebted to Drs. Maurice Giroux, Edouard Morin and Robert Garneau, pathologists, and to Drs. J. A. Gravel and Maurice Beaulieu, thoracic surgeons.

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RÉSUMÉ

La blastomycose nord-américaine ou dermatite de Gilchrist est relativement rare dans la région de Québec. Les quelque vingt cas rapportés depuis 1938 étaient surtout du type cutané. Le traitement le plus récent de cette affection repose sur l'emploi des diamidines aromatiques dont la dernière à date est la 2-hydroxystilbamidine. Cette dernière n'entraînerait pas les complications névralgiques du trijumeau qu'on a déjà notées à l'administration des autres membres de ce groupe de médicaments. L'auteur présente ses observations personnelles dans le traitement de trois malades atteints de cette mycose. Les résultats furent assez satisfaisants et les incidents du traitement de peu d'importance.

EMERGENCY RESECTION AND ANASTOMOSIS FOR PERFORATED SIGMOID DIVERTICULITIS

In reporting cases of perforated diverticulitis from Melbourne, primary resection of the sigmoid colon is recommended as the preferred treatment for ruptured diverticulitis. The patients are often elderly, colostomy is not curative, and the disease recurs or becomes a chronic diverticulitis with complications. There are two types of diverticulitis: in one there is no history of bowel symptoms and in the other bowel symptoms with peridiverticulitis have been of long duration. Emergency sigmoidectomy is safe if the patient is otherwise well, the colon is mobile and there is no intestinal obstruction. In advanced general peritonitis, no operation is worth while. No attempt is made to resect all the diverticula-bearing colon.—P. Ryan: *Brit. J. Surg.*, **45**: 611, 1958.