Some Factors Affecting Survival in Systemic Blastomycosis*

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The finding of over 200 proved cases of blastomycosis in the state of Kentucky has afforded interesting material to study the survival rates and factors affecting survival rates in this systemic fungus disease. The question of survival in blastomycosis is still subject to some controversy since in the original series reported by Martin and Smith of 117 cases in 1939, some 92 per cent of whom were dead within five years. On the other hand, in the Veterans Administration series reported in 1964, only about a quarter had died in the period of followup of up to 16 years. Sutliff et al reported about the same figure (28 per cent) in two to four years. It has not been possible to carry out careful follow-up over a number of years, and the effect of such factors as age, treatment and type of disease has not been evaluated. It is the purpose of this paper to attempt to evaluate some of these factors in the prognosis of this disease.

MATERIALS AND METHODS

The first case of blastomycosis was found in Kentucky in 1922. Between then and 1949 a total of 25 cases were found. Between 1950 and 1953, the number averaged about six per year, and since 1954, the number has averaged about 12 per year with considerable consistency. Thus, there were available when we started our studies in the summer of 1965 over 200 cases of proved blastomycosis in Kentucky. Of these, follow-up studies could be performed on a total of 186. A description of the prevalence of blastomycosis in Kentucky and its location and type of disease has been published.

All cases were proved either by culture or by pathologic examination, and an attempt was made by home visits and follow-up in every possible way to locate every case. In addition to attempted home visits, a search of death records at the Division of Vital Statistics of the State Department of Health was conducted for all cases in which a death was suspected or known to have occurred or in which the patients could not be located. When a death record was obtained, copies of the certificate were obtained and an attempt was made to find out whether the blastomycosis had been active or inactive at the time of death or was the cause of death or not. For this purpose, the death records were relied upon.

During the visit, an inquiry was made into the state of the patient’s health, whether he had been hospitalized since diagnosis, whether he was healed, inactive, whether he was able to work and many other questions. In addition, the local physician was contacted in regard to the kind and amount of treatment and whether the patient had progressed or reactivated during his care. This material was then put together and summarized. Hospital records on these cases were also reviewed and wherever possible direct ascertainment of the amount of therapy received was verified from hospital records.

In considering treatment, a patient was classified as treated with either amphotericin B, stilbamidines (including 2-hydroxystilbamidine), iodides, and the remainder as “other and no treatment.” If a patient was treated with more than one form of therapy, he was classified in the highest groups as outlined above—that is, if he received both iodides and amphotericin B he was classified in the amphotericin B group. This automatically meant that the more severe and recurring diseases were classed in the first two forms of therapy and the milder types in the latter two.

RESULTS

Figure 1 shows the distribution of proved cases in Kentucky based on 182 cases and the high prevalence in the central part of the state in the areas of Louisville and Lexington. While it is true that medical centers are located here, it is also apparent that there is a considerable concentration of cases, at least around Lexington in the central Kentucky area. Figure 2 shows the status on anniversary of 186 cases during the first five years of followup. It is seen from this figure that 20 per cent of the cases had died from blastomycosis during the five year follow-up, 7 per cent had progressed and 10 per cent had died of other diseases. Overall then, blastomycosis carries a serious prognosis involving more than 30 per cent deaths in the course of five years after diagnosis.

When one comes to analyze the factors affecting this death rate it turns out that there are many variables involved, among which are age, type of disease and type of treatment. The analysis of these three factors individually and together makes the study rather complicated.

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*The life table analysis followed the technique of Bosworth and Alling.
Comparisons by race are shown in Figure 3. It is seen that among 150 white and 26 non-white patients, the rate of survival and progression is quite similar in the two races. Thus, although the disease is a little more prevalent among Negroes on a percentage basis, apparently the prognosis of the disease once it is acquired is no different in the Caucasian than in the Negro.

Co-existence of Tuberculosis: Figure 4 shows the comparison of 162 cases who did not have complicating tuberculosis compared to the prognosis of 24 cases who had both tuberculosis and blastomycosis. It is seen that the deaths from blastomycosis more than doubled in the presence of tuberculosis and the progression almost tripled. It is therefore seen that the presence of both diseases has a markedly detrimental effect on the prognosis of the disease.

Age: In Figure 5 are shown the effects of age on the prognosis. It is seen that there were 33 cases in the 0–39 group, 83 in the 40–59 group and 66 in the 60–99 year age group. The difference in prognosis is markedly related to age. Thus, 3 per cent of the young group had died of either blastomycosis or other disease, 27 per cent of the 40–59 year group, and 50 per cent of the older age group dur-

FOLLOW-UP AT FIVE YEARS
BY RACE

| Died of Other | 17.4% |
| Died of Blast | 22.2% |
| Progressed   | 5.0%  |
| Did Not Progress | 55.5% |

Figure 3
and depends on diagnosis made with varying quality of medical competence so that it is probably only relatively accurate, but it does seem to indicate that the skin only type does have a better prognosis than either of the other two types. This is apparent since 77 per cent of the skin only type did not progress in contrast to 61 per cent of the cases without skin involvement, and only 54 per cent of the cases with skin and other involvement. The deaths from blastomycosis and other diseases in the cases without skin involvement, or with skin and other involvement are 31 and 35 per cent in contrast to only 17 per cent among those who had only skin involvement. Similarly, progression is less in this group in contrast to the other two groups.

**Type of treatment:** In Figure 7 are seen comparisons of the total group by different types of treatment. It was found after extensive analysis that only three groups could be separated from the no-treatment group. These consisted of stilbamidine and 2-hydroxystilbamidine, 20 cases; amphotericin B, 70 cases; and iodides, 22 cases. The other and no-treatment group, which included one case of vaccine treatment, several cases of cautery only and several of surgery, were simply classified as no-treatment. It is seen that the results are not as different as one would expect. The greatest proportion showing progression (12 per cent) were in the stilbamidine group, whereas the no-treatment group showed the lowest proportion of progressive cases (1.7 per cent). When this is analyzed further, death either from blastomycosis or other causes made up

**Type of disease:** In Figure 6 is seen a comparison of the prognosis with three different types of disease. Fifty-five cases who had involvement of the skin only, 67 who had involvement of the skin with other organ involvement and 63 cases who did not have skin involvement are compared. It must be remembered that this is a rather crude definition

**Figure 4**

**FOLLOW-UP AT FIVE YEARS BY AGE GROUP**

| Died of Other | 0.0% | 4.5% |
| Died of Blast | 3.0% | 0.0% |
| Progressed | 9.0% | 12.0% |
| Did Not Progress | 81.0% | 81.0% |

**Figure 5**

**FOLLOW-UP AT FIVE YEARS BY TYPE**

| Died of Other | 12.0% | 12.0% |
| Died of Blast | 20.0% | 10.0% |
| Progressed | 31.0% | 31.0% |
| Did Not Progress | 77.0% | 77.0% |

**Figure 6**

**Figure 7**

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34 per cent of the stilbamidine group, 25 per cent of the amphotericin B group, and 20 per cent of the iodide group. On the other hand, the iodide treated group showed the greatest proportion of arrested cases (74 per cent) though this was not markedly different from the 68 per cent of arrested cases in the amphotericin group. Surprisingly enough in those who received other and no treatment, although almost one-third died, 66 per cent were arrested. Substantially more in this no-treatment group died of blastomycosis (26 per cent) than in the stilbamidine, amphotericin or iodide groups (17, 16 and 10 per cent respectively).

Analysis was made to determine if those receiving no treatment or iodides were mostly milder (skin only type) or in the younger age group. There was no significant difference in age among those receiving iodides and no treatment compared with those receiving stilbamidine or amphotericin B. There was a significantly greater percentage of the skin only type who received no treatment or iodides compared to the other types of disease.

**Combined Consideration of Type of Disease and Treatment:** Comparison of skin only type of disease by treatment groups is found in Fig 8. This includes 27 patients who had other or no treatment, nine patients treated with only iodides, 15 patients treated with amphotericin B and five patients treated with stilbamidine. It is seen from Fig 8 that the skin only type had good prognosis regardless of the type of treatment, since 76 per cent of the type of disease did not progress even without treatment. There was no progression in 80 per cent of the cases treated with stilbamidine, 87 per cent with iodides and 90 per cent with amphotericin B. On the whole it seems quite clear that the prognosis is good when only the skin is involved in blastomycosis. Actually, of the 56 cases of this type, 27 (48 per cent) received essentially no treatment.

Comparison of the follow-up at five years of the cases that had skin and other involvement is seen in Fig. 9. It is seen that the prognosis does not appear as good as when only the skin was involved. In contrast to 48 per cent without treatment in the skin only type, only 18 of 67 (27 per cent) were not treated in this group. The worst prognosis appeared in the nine cases treated with stilbamidine in which more than half the patients died and one-sixth progressed in the five-year period. Even with amphotericin B, 31 per cent of the patients died and 6 per cent progressed. Thus it seems clear that this type of involvement (skin with other organs) had a distinctly worse prognosis than the skin only type.

Figure 10 illustrates the results of follow-up of 63 cases that did not have any skin involvement classified by the type of treatment. It is seen that 29 (46 per cent) of these cases received no treatment. Only two cases were treated with iodides and six cases with stilbamidine so that the results with these two groups are too small for serious comparison. On the other hand, comparing the 26 cases...
that received amphotericin B and the 29 cases that had other or no treatment it is startling to see that the percentages that did not progress in these two groups are quite similar (60 versus 58 per cent). It is seen, however, that deaths are markedly different in that 42 per cent of the no treatment group died in five years compared to 27 per cent of the amphotericin group. However, if deaths and progression are added, the two groups are almost equal in results.

Type of Disease and Age: In Figure 11 comparisons are made of three factors—age, type of disease and outcome. Here it is seen that the prognosis is better in the younger age group than in the older age groups regardless of the type of disease. On the other hand, if one looks down each column, it is seen that the skin only type does seem to have a better prognosis than either of the other two types in any given age group.

Comparison of Type of Disease with Type of Treatment: In Figure 12 comparison is made of the type of disease and the four types of treatment, stilbamidine, amphotericin, iodides and other and no treatment. Here again, the skin only type does seem to have a better prognosis than the other types. The other two types do not seem to differ markedly in results, although there is a suggestion that the type involving the skin and other organs might have a more serious prognosis than the “other types of organ involvement,” since only 27 per cent of this group were not treated compared to 46 per cent of the latter group.

Treatment with Amphotericin: Some interesting figures are derived from the comparisons of the group that was treated with amphotericin B by the amount of the drug received. Figure 13 shows a comparison of 74 patients who received other treatment or no treatment with 19 patients who received less than 1 gram amphotericin. It is seen that the prognosis is, if anything, a little worse in those patients who received a small amount of amphotericin than with no treatment since one-third of those without any treatment died, whereas almost half (48 per cent) of those with a small amount of amphotericin died. It is possible, however, that more severe cases were selected for amphotericin therapy. In Figure 14 are illustrated the results with larger doses of amphotericin. Here are compared the results with 21 cases treated with be-
between 1 and 2 grams and 19 cases treated with 2 grams or more. It is evident that with a larger dosage of amphotericin (1 gram or over) the results appear markedly improved over the lower dosages or no treatment. Only 15 per cent, though, of the total group died, of which only 5 per cent were of blastomycosis and 11 per cent of other diseases. In the group who received 2 grams of amphotericin, there had been only one death among 19 cases in five years and that was of other than blastomycosis. In summary, the comparison of the results of treatment with 1 gram or more of amphotericin with the results with "other and no treatment" makes clear the desirability of adequate treatment.

**Summary**

Based on the follow-up of almost 200 cases of North American blastomycosis in the state of Kentucky, some extremely interesting generalizations can be made about the seriousness of this disease.

1. In the group as a whole at the end of five years after diagnosis, one-fifth of the patients had died of blastomycosis and an additional 11 per cent had died of other causes. It is quite clear, therefore, that this disease is a serious disease and that the mortality figures formed in follow-up are comparable with those observed with systemic histoplasmosis.

2. Although tuberculosis was present in only 13 per cent of the cases, it markedly worsens the prognosis for both death and progression, the rates being twice those of persons who do not have both diseases.

3. It is apparent from analysis of the figures that the factors of age, type of disease, type of therapy and amount of therapy have a great deal of influence on the outcome.

4. When the disease involves only the skin, there does appear to be a better prognosis than when it involves the skin with other organs or does not involve the skin. While this may be an artifact created by the fact that many mild cases show skin involvement only, it does seem to be fairly clear in comparing the three groups that those with skin involvement only had a better prognosis than the other types.

5. Age exerted a marked influence on the mortality from the disease since only 3 per cent of the youngest group died within five years after diagnosis whereas 27 per cent of the 40-49 year group had succumbed compared to 50 per cent of the oldest age group.

6. The type of treatment did not seem to have as marked an effect as either of the other two factors, but this was extremely difficult to evaluate because
it would appear that the more severe cases were moved up from no treatment to iodides to stilbamidine to amphotericin. Thus, the more severe cases would receive the more elaborate treatments. For this reason, when the gross figures are compared as in Figure 7 it is seen that the overall deaths following treatment with stilbamidine or amphotericin are relatively high (35 and 25 per cent) in comparison to 20 per cent for iodides and 33 per cent for other and no treatment. Thus, the general position of other treatment and no treatment and iodides is relatively enhanced in this group since only the mildest cases would receive no treatment.

7. It is clear that the results of treatment with amphotericin B are closely related to the amount of amphotericin given and that less than 1 gram is ineffective. The results are quite satisfactory with dosages over 1 gram and even a little better with dosages of 2 grams or more.

In conclusion, it is obvious that the earlier estimates of 90 per cent mortality in five years were excessive but that the mortality and severity of blastomycosis are by no means to be ignored but represent a complicated mixture of type of disease, age of patient and type of treatment. It is hoped that this study will stimulate others to gather further data.


As I was preparing this chapter for the memorial volume to Doctor Charles E. Smith, I received notice of the death of Doctor William A. Winn, I cannot refrain, therefore, from referring to my strong debt to both Doctor Smith and to Doctor Winn and to my feeling of loss at their leaving the scene of their endeavors. Doctor Smith was stimulating, encouraging and enthusiastic in his support of anything relating to the mycotic field. From the very earliest days of our interest in histoplasmosis he supported and encouraged this work. His work in coccidioidomycosis is well recognized, but his continual stimulation and support of all research in mycology should be long remembered.

Doctor Winn was an earnest and sincere student of tuberculosis and coccidioidomycosis and a wonderful and dedicated physician. He is responsible for many of the early studies in coccidioidomycosis, particularly those relating to clinical studies, and was instrumental in developing the intrathecal treatment of coccidioidal meningitis which has resulted in the saving of many lives, including that of my brother. Doctor Winn and I traveled together to Japan, and we were intimate friends for many years. His loss and that of Doctor Smith are tremendous blows not only to mycology but to research and medical science in general.

REFERENCES


