

Clinical Trial of Butylphenamide in the Treatment of Certain Varieties of Ringworm

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THIS report concerns the topical use of butylphenamide* in the treatment of some of the common varieties of ringworm of the scalp and body. Laboratory data dealing with fungicidal effect "in vitro" and the absence of signs of toxicity in experimental animals suggested that butylphenamide would be a more valuable fungicide than any of the many others available. Our clinical impression is that this is so.

Ideally all clinical trials should be carried out under strict statistical control, but from a purely practical point of view this is not possible when dealing with local applications which might be of value in the treatment of the various kinds of ringworm. This is so because the duration and response to treatment will vary with the type of fungus responsible and with the part of the body affected, and possibly with the type of skin which the patient has, ringworm being on the average rather more long lasting on a dark "hairy" skin than on a fair skin. The age of the patient may influence results, since we know that ringworm in babies clears relatively quickly. There is also good reason to believe that some fungi tend to lose virulence on transfer from one individual to another—and this will influence treatment results. Again, some patients will produce inflammatory and quickly clearing lesions, while others infected by the same fungus will react with chronic and indolent lesions. Finally, it is rare indeed to see ringworm lesions symmetrically distributed on the body, so that using the method of paired comparisons is impractical.

Therefore, no apology is offered for presenting what is little more than a series of clinical impressions regarding the usefulness or otherwise of butylphenamide tincture and ointment. However, the cases included in the trial were limited to those common infections which had been seen so often that one felt that a really beneficial response to treatment would be noticeable when the results of a series were compared with past results—and colour photographs were taken of all cases at each attendance. Only those patients who attended as and when required until their ringworm was quite clear are included.

Derivatives of salicylic acid and of salicylamides are known to possess fungistatic activity. Good results have been claimed from the use of preparations of sali-

*A preliminary report on the use of butylphenamide as a fungicide was read, in co-operation with Dr. John Krafchuk, at the Eleventh International Congress of Dermatology, in Stockholm, in August, 1957.

cylanilide and carbowax for the treatment of *Microsporum audouini* scalp infections (Schwartz, et al., 1946, Brain, et al., 1948, and Haber, et al. 1949), but Beare and Cheeseman (1951) were unable to confirm these results "when the spontaneous cure rate of *M. audouini* tinea capitis is borne in mind." A number of substituted salicylamides were synthesized by Jules, et al. (1956). N-n-butyl-3-phenylsalicylamide (butylphenamide) was later screened for its microbiological activity by Hok, et al. (1956). These authors reported that this substance, when compared to other anti-fungal agents commonly used in treatment appeared to be more active. They also produced evidence showing that *Trichophyton mentagrophytes* and *M. audouini* did not develop resistance to the substance. The toxicity of butylphenamide in animals has been studied by Seeberg, et al. (1956) who reported that large amounts of butylphenamide applied to the skin of rabbits every day for a month did not cause any significant change in blood, urine or gross or microscopic appearance of tissues. They also reported that very little butylphenamide was absorbed from the gastro-intestinal tract of animals. Krafchuk (1956) and, independently, Keddie, et al. (1956) have reported encouragingly on the use of butylphenamide in skin eruptions due to dermatophytes. Krafchuk, in addition, found an antipruriginous effect in certain skin diseases which were not due to ringworm infections, such as lichen simplex chronicus, atopic eczema and contact dermatitis.

The trial was started in June, 1956, and all cases of ringworm, except infections due to *M. audouini*, seen from this date to March, 1957, were included initially in the trial, and were given some preparation of butylphenamide. Children with *M. audouini* infections were excluded because, in my opinion, the essential thing here is to render the child non-infectious at the earliest possible opportunity, and for this X-ray epilation is necessary. Since all our *M. audouini* infections now come from foreign lands, it is our ambition to keep our area free of this infection. Only those patients who had attended regularly when requested and to complete cure, and who had a common variety of infection, the response to treatment of which we could reasonably compare with past results, were included. Eventually, the final analysis consisted of forty-three cases of infections due to *Microsporum canis*, *Trichophyton sulphureum* and *Trichophyton discoides*. In all these cases the causative fungus had been isolated by mycological culture.

CLINICAL RESULTS.

(a) *Microsporum Canis*.

There were eleven cases of scalp infection. One of eight weeks' duration developed a kerion after two weeks' treatment, and butylphenamide was stopped. Another of three weeks' duration developed a moderately severe inflammatory reaction after two weeks' treatment. His condition was clear five weeks later, but butylphenamide was discontinued for ten days at the height of the reaction.. In a third case after five weeks' treatment it was considered necessary to carry out X-ray epilation, since there was no change in the boy's condition and there was some danger of spread of infection to his many brothers and sisters. In a fourth, X-ray epilation had been recommended, but the parents refused to give consent,

and this was after butylphenamide had been used for a period of eleven weeks without clinical change. All these four cases were regarded as failures. Of the other seven cases, one of six weeks' duration showed no inflammatory reaction and cleared in seven weeks, three showed mild inflammatory reaction and cleared in periods of four weeks (initial duration one week), five weeks (initial duration three weeks), and seventeen weeks (initial duration one week). Two showed a moderate inflammatory reaction and cleared in periods of eight weeks (initial duration two weeks), and seven weeks (initial duration three weeks), respectively, and one showed a severe reaction and cleared in four weeks (initial duration three weeks).

TABLE 1.
MICROSPORUM CANIS.

Case No.	Sex	Age	Parts affected	Degree of reaction (0 —++++)	Duration before treatment (weeks)	Duration of treatment (weeks)	Assessment of result
1	F	10	Scalp	++++	8	2	Failure
2	M	11	Scalp	+++	3	5	Failure
3	M	4	Scalp	+	1	5	Failure
4	M	5	Scalp	+	±6	11	Failure
5	F	5	Scalp	0	6	7	Good
6	M	9	Scalp	++	1	4	Good
7	F	8	Scalp	++	3	5	Good
8	M	6	Scalp	++	1	17	Indefinite
9	F	3	Scalp	+++	2	8	Good
10	F	3	Scalp	+++	3	7	Good
11	M	10	Scalp	++++	3	4	Good
12	F	37	Body and limbs...	+++	1½	4	Good

In addition, there was one adult patient with a very severe tinea corporis due to *M. canis* affecting large areas on trunk, arms and legs. Her condition, present for ten days before treatment, cleared completely in another four weeks.

It is suggested that these results in *M. canis* infections are as good, if not better than one would get from any other type of local application.

(b) *Trichophyton Sulphureum*.

There were eight cases of tinea capitis. Four non-inflammatory cases we regarded as failed, one (of two weeks' duration) after twenty-six weeks' treatment, when X-ray epilation had to be carried out; the second (of four weeks' duration) after twenty-six weeks' treatment, when the condition was really still active; the third (of one week's duration) after nine weeks' treatment, when X-ray epilation had to be carried out, and the fourth (one week's duration) after six weeks' treatment, when there was no change and X-ray epilation was carried out (an associated tinea corporis cleared within six weeks). One boy who had had a mild infection for five weeks cleared in a further eleven weeks' treatment. Two children had had the

infection for five months; one of these cleared in ten weeks, the other in twelve weeks; the former was non-inflammatory, but after two weeks' treatment developed a moderately severe inflammatory reaction, the second was non-inflammatory at the beginning but later developed a kerion. We would regard these cases as failures. The last case had an infection of thirty-one weeks' duration but had a moderately severe reaction from the start. He cleared with three weeks' treatment (probably good luck, since the infection was likely to be clearing by this time any how).

TABLE 2.
TRICHOPHYTON SULPHUREUM.

Case No.	Sex	Age	Parts affected	Degree of reaction (0 - + + + +)	Duration before treatment (weeks)	Duration of treatment (weeks)	Assessment of result
1	...	M	...	10	...	Scalp	... 0 ... 2 ... 26 ... Failure
2	...	M	...	9	...	Scalp	... 0 ... 4 ... 26 ... Failure
3	...	F	...	8	...	Scalp	... 0 ... 1 ... 9 ... Failure
4	...	F	...	9	...	Scalp	... 0 ... 1 ... 6 ... Failure
5	...	M	...	12	...	Scalp	... + + ... 5 ... 11 ... Failure
6	...	F	...	6	...	Scalp	... + + + ... 20 ... 10 ... Failure
7	...	F	...	10	...	Scalp	... + + + + ... 20 ... 12 ... Failure
8	...	M	...	8	...	Scalp	... + + + ... 31 ... 3 ... Questionable
9	...	F	...	11	...	R. neck	... + + + ... 1 ... 4 ... Good
10	...	F	...	8	...	R. arm	... + + + ... ½ ... 4 ... Good
11	...	M	...	10	...	L. neck	... + + ... 1 ... 3 ... Good
12	...	M	...	10	...	R. arm	... + + ... 1 ... 4 ... Good
13	...	F	...	8	...	L. arm	... + + ... 2 ... 4 ... Good
14	...	M	...	10	...	R. cheek and ear...	... + + ... 8 ... 4 ... Good
15	...	F	...	12	...	Front of chest	... + + ... 6 ... 6 ... Good
16	...	F	...	12	...	R. neck	... + + ... 11 ... 3 ... Good

There were eight cases of tinea corporis of which two had a moderate reaction; they both cleared within four weeks. The other six had mild reactions. One (one week's duration) cleared in three weeks, three (durations one week, two weeks and eight weeks) in four weeks, one in six weeks (duration six weeks) and one in eleven weeks (duration three weeks). We would regard these eight cases as being successfully treated by butylphenamide.

(c) *Trichophyton Discoides*.

Five cases of tinea capitis all of which showed severe kerions. Three children with durations of one month, two weeks and ten days, cleared in five weeks, six weeks, and two weeks, respectively, and one with a duration of three months cleared in three weeks. The other boy had an exceptionally severe tinea capitis of three weeks' duration. Butylphenamide was only one of many applications used in his long

illness of sixteen weeks' duration, from the first time seen, but it was one of the most useful. These results were considered good.

Three cases of tinea barbæ were included. One of eight weeks' duration cleared in three weeks, one of two weeks' duration cleared in seven weeks, and one of four weeks' duration cleared in seven weeks. All were severely inflammatory. These results are good.

There were eight cases of tinea corporis. One severe reaction in a boy of ten and of four weeks' duration, cleared in two weeks. Five had moderate reactions, and

TABLE 3.
TRICHOPHYTON DISCOIDES.

Case No.	Sex	Age	Parts affected	Degree of reaction (0 — + + + +)	Duration before treatment (weeks)	Duration of treatment (weeks)	Assessment of result
1	M	5	Scalp	+++ +	4	5	Good
2	M	9	Scalp	+++ +	2	6	Good
3	M	6	Scalp	+++ +	1½	2	Good
4	M	8	Scalp	+++ +	12	3	Good
5	M	4	Scalp	+++ +	3	16	Useful in a difficult case
6	M	18	Beard	+++ +	8	3	Good
7	M	35	Beard	+++ +	2	7	Good
8	M	42	Beard	+++ +	4	7	Good
9	M	10	R. shoulder R. leg	+++ +	4	2	Good
10	M	9	L. knee	+++	3	2	Good
11	F	2	Back of trunk	+++	3	2	Good
12	F	17	L. shoulder L. arm	+++	1	4	Good
13	F	12	R. shoulder R. back	+++	1	4	Good
14	F	13	Upper back	+++	3	3	Good
15	M	22	L. back of hand	+++ +	2	3	Developed pompholyx
16	F	19	Face R. arm R. shoulder	+++ +++ +++	2 1	3 2	Good (did not treat face initially)

two of these, each of three weeks' duration, cleared in two weeks, two, each of one week's duration, cleared in four weeks, and one of three weeks' duration cleared in three weeks.

Two further cases of tinea corporis were of some interest. One of two weeks' duration, affecting the back of the hand, seemed to do very well after one week's treatment, but then the patient developed a pompholyx reaction on both hands.

This settled in a further fortnight. And another patient, with ringworm of one week's duration affecting the face, the right arm and shoulder, applied tincture of butylphenamide to the arm and shoulder and after one week there was much improvement. The face, however, had become worse and on questioning it turned out that she had not put butylphenamide on to her face, having mistaken the instructions which she was given. After a further three weeks of treatment her condition was completely clear.

CONCLUSIONS.

1. *Microsporum Canis* : Lesions of the non-hairy skin clear quickly and, I believe, quicker than they would do so spontaneously. Lesions of the scalp cleared quickly in about half the cases treated, but in the other half there did not appear to be any beneficial effect.
2. *Tirchophyon Sulphureum* : There was nothing gained from the treatment of the scalp infections, which in this particular series were all non-inflammatory. However, lesions on non-hairy skin cleared quickly.
3. *Trichophyton Discoides* : Here there were most useful results, and the duration of these inflammatory infections appeared to be substantially shortened. All the scalp infections in the series, except one, cleared in six weeks, and in the case which did not clear, butylphenamide was the most useful fungicide of several used. The beard infections cleared within seven weeks, and the lesions of the non-hairy skin within five weeks.

Adverse Effects : There were no examples of epidermal sensitivity nor of primary irritation in this series, nor indeed in any of the other patients treated with butylphenamide but not included in those analysed here. Krafchuk (1957) has not yet seen any example of sensitivity. However, the tincture occasionally stings and young children may object to its application.

Unfortunately, butylphenamide causes a greenish-blue fluorescence in Wood's light, which makes examination of scalp infections due to microspora difficult but, of course, this fluorescence is not limited to the hair.

SUMMARY.

Butylphenamide is a most useful fungicide without any adverse effects. One's clinical impression is that it is superior to any of the older preparations in common use. However, there was no evidence obtained from this trial that it is likely to have any part to play in the treatment of non-inflammatory scalp ringworm.

My colleague, Dr. Ivan H. McCaw, kindly referred some of the cases; Dr. Jacqueline Walker, of the London School of Hygiene and Tropical Medicine, did all the mycological work and identified the fungi; Mr. Ronald Woods, Medical Photographer, Royal Victoria Hospital, took a great many photographs; Dr. John Krafchuk, of New Orleans, U.S.A., suggested the trial and arranged with Dr. Edwin McLean of Cutter Laboratories Limited, U.S.A., that supplies of butylphenamide be sent. The preparation was supplied under the trade name "Bynamid" (Bynamid Ointment is a five per cent. mixture of Bynamid in a carbowax-polyethylene glycol base; Bynamid Tincture is five per cent. solution of Bynamid in a mixture of isopropyl alcohol, acetone prophylene glycol, and Aerosol).

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REVIEW

AORTOGRAPHY: ITS APPLICATION IN UROLOGICAL AND SOME OTHER CONDITIONS. By W. Barr Stirling, Ch.M., F.R.C.S.(Ed.), F.R.F.P.S.G. (Pp. vii + 291; figs. 155. 50s.) Edinburgh and London: E. & S. Livingstone, 1957.

IN this volume the author has summarized his personal experience of five hundred aortograms performed for the investigation of various renal conditions.

The opening chapters give an historical survey of the methods used, a discussion of the surgical anatomy of the renal arteries, and a description in detail of the particular technique used by the author.

The book is admirably illustrated with aortograms showing the abnormal vascular patterns produced in various lesions. Interesting chapters are given on the interpretation of the films and of the hazards and complications that may result from these investigations.

The book gives a very comprehensive survey of the subject, and it certainly should be in the library of every surgeon, especially those surgeons interested in urological work. J. M. M.