IMPETIGO CONTAGIOSA
IN THE ARMY, TREATED WITH MICROCRYSTALLINE SULPHATHIAZOLE

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THE Official Medical History of the War 1914–18 recorded that the maladies included under the term "impetigo" provided the largest number of cases of skin-disease admitted to medical units. During the present war, although much has been done by hygiene officers and unit medical officers to prevent them, the incidence of impetiginous conditions has been high; therefore, to reduce to a minimum the loss of man-days, those engaged in the cure of skin-disease have tried to accelerate therapy to the greatest degree compatible with the well-being of their patients.

A constant watch has been kept on medical publications for new methods of therapy apparently suitable for military practice. The claim of Harris (1943) that "a single application of a new physical form of the sulfonamides in the treatment of impetigo in my experience with the method thus far has been found to cure the lesions within a day and to stop the spread of the disease," obviously demanded attention. Harris used a 20% suspension of microcrystalline sulphathiazole; and, although his published results appeared to refer entirely to children, his claim was sufficiently strong to merit investigation. Therefore arrangements were made for a clinical trial of the drug in the Army. Owing to the difficulty in obtaining supplies, a 15% suspension in normal saline was used. The investigation was undertaken and reported by Bigger and Hodgson (1944), who found that of 50 cases of impetigo contagiosa treated with microcrystalline sulphathiazole 48 were cured in an average of 5·3 days; of 25 cases treated with local applications of a 15% suspension of the ordinary form of sulphathiazole in normal saline containing 4% tragacanth 23 were cured in an average of 6·5 days. One patient treated with microcrystalline sulphathiazole developed sensitivity to the drug. In their opinion, treatment with the new form of sulphonamide was a definite advance in the therapy of impetigo contagiosa.

Experience has shown that the results obtained by investigators bringing special skill and enthusiasm to a clinical inquiry are not invariably obtained by all clinicians when the new technique is made generally available. Therefore it was necessary to discover if the results claimed by Bigger and Hodgson could be obtained in most military hospitals in the UK to a sufficient extent to justify the use of microcrystalline sulphathiazole as a standard army treatment for impetigo. To obtain this information a large-scale trial had to be carried out critically with full controls, and the standards of diagnosis, assessment, and cure had to be as uniform as possible. After consultation it was agreed that the problem might properly be assessed by statistical methods.

The dermatologists who coöperated in the investigation were instructed that the cases chosen for the inquiry were to be uncomplicated examples of impetigo contagiosa. Cases of eczema or dermatitis secondarily impetiginised and patients who had become sensitised to sulphonamides before admission to hospital were to be excluded. Briefly it was the effect of microcrystalline sulphathiazole on the impetigo contagiosa of Tilbury Fox (1864) which was to be assessed.

The first point to be noted was that, despite the relatively large number of cases of eruptions of the face labelled impetigo which were referred to the hospitals concerned, true examples of impetigo contagiosa of the type required were not very common. The report suggests that the ratio of classical impetigo of Tilbury Fox to other forms of septic eruptions of the face is approximately 1 to 2 (1270 to 2400); but this is a little misleading, as the 2400 possible cases of impetigo were to some extent selected before reference to hospital, and the ratio between classical impetigo contagiosa and other impetiginous eruptions is probably much lower.

In the 1914–18 war impetigo was divided into four classes: impetigo contagiosa, ecthyma, impetigo secondary to scabies, and infected seborrhœic eczema. This differentiation holds good today but cannot be accepted without qualification for the impetiginous eruptions affecting the face, with which we are at present concerned. All the dermatologists complained that true impetigo was rarer than was supposed, that there was difficulty in getting cases suitable for the trial, and that the investigation would have to continue for a longer period than had originally been anticipated if a significant number of cases was to be obtained. In these complaints lies a clue to the reports received from other sources on many other occasions that many cases of so-called impetigo were not cured either with sulphonamides or with penicillin.

Objections were raised against lotio cupro-zincica as the standard control, but it was chosen because it was well known and often used both in military and in civilian practice, and an estimate of its efficiency would be useful.

METHODS OF INVESTIGATION

The investigation was made in the UK January–November, 1944. Sixteen military hospitals were asked to select for the experiment their next 150 consecutive uncomplicated cases of impetigo contagiosa. Each hospital allotted 50 of its chosen cases to each of the three treatments described below, the allocation being serial—i.e., case 1 to treatment A, 2 to B, 3 to C, 4 to A, and so on. The treatments were as follows:

A. Microcrystalline sulphathiazole in 15% suspension.
B. Ordinary sulphathiazole in 15% suspension.
C. Lotio cupro-zincica.

The following instructions were issued:

Treatment "A," with microcrystalline sulphathiazole.—The patient's face and neck are cleansed, his beard shaved or clipped, and the crusts removed from the lesions. On the first occasion the suspension is applied all over the area—e.g., face—to prevent further lesions on untreated areas. On subsequent occasions the crusted areas only are treated, care being taken that the powder-crust formed on the lesions is not removed. The treatment is given twice daily. When the patient is judged sufficiently recovered, zinc cream or Lassar's paste may be applied to save a day or so of the period of treatment. To lessen the risk of sensitisation, microcrystalline sulphathiazole should not be applied to any lesion for longer than ten days.

Treatment "B," with ordinary sulphathiazole.—After preparing the area as described for treatment A, apply a saline suspension of ordinary sulphathiazole 15%, tragacanth 4%, and normal saline to 100%. Treatment should be given twice daily, and should approximate as closely as possible to the routine described for treatment A.

Treatment "C," with lotio cupro-zincica.—Prepare the area as for treatment A and treat the lesions (on the first day the whole of the area) with lotio cupro-zincica (copper sulphate gr. 4, zinc sulphate gr. 6, and camphor water to 1 fluid oz.). The lesions should be thoroughly swabbed with the lotion for two minutes four times daily and thereafter are usually best left exposed to the air.

The hospitals were instructed not to give sulphonamides concurrently by the mouth to patients under investigation. Cases were to be regarded as cured when the skin appeared normal or only very slightly erythematous, so that treatment could be discontinued without a relapse occurring. The data were to be recorded on suitable cards and forwarded to us for analysis.

RESULTS

After ten months we received only some 1270 out of a possible 2400 cards from fourteen of the sixteen hospitals. We had to discard 150 cards, for in comparing the treatments we had to rely on the total time spent in hospital, and where a patient had some other disease besides impetigo he could not be included in the analysis.

We had originally intended to use a more elaborate method of statistical analysis, because there were such differences in the consistency of the results that it was evident that the random errors varied not only with the different treatments but also with the different hospitals. Hence it would not be legitimate to pool the data to obtain a single estimate of the random errors for the whole experiment. We had also expected that the longer a patient had had impetigo before admission to hospital, the longer would be his cure. We therefore obtained for each case the approximate number of

TABLE I—DETAILS OF RESULTS

Hospital	1			2			3			4			5			6			7			8		
Treatment	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
Successes	18	22	17	13	15	4	15	16	15	9	10	8	12	13	11	28	39	39	34	38	38	27	27	26
Failures	2	..	1	4	2	11	1	2	1	..	..	1	..	2	4	7	8	8	5	3	1	3	3	3
Discarded cases	17	10	22	1	1	..	4	2	4	1	2	1	5	2	1	3	1	3	4	2	2	6	7	8
Total	37	32	40	18	18	15	20	20	20	10	12	10	17	17	16	38	48	50	43	43	41	36	37	37
Aver. days' stay of successful cases	14·4	14·5	13·2	11·5	12·8	13·0	10·6	10·9	10·9	7·2	6·9	7·5	11·75	11·1	13·4	11·4	12·6	11·5	11·9	12·8	15·1	11·3	12·2	14·6

Hospital	9			10			11			12			13			14			Total		
Treatment	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
Successes	43	44	40	36	37	28	41	41	42	7	6	6	22	23	21	17	16	17	322	347	312
Failures	1	1	6	14	13	22	..	1	..	..	..	..	..	..	1	1	3	2	38	38	61
Discarded cases	5	5	5	..	..	..	..	..	1	..	1	1	7	4	8	2	..	1	55	37	57
Total	49	50	51	50	50	50	41	42	43	7	7	7	29	27	30	20	19	20	415	422	430
Aver. days' stay of successful cases	9·2	10·9	11·0	11·75	11·3	12·8	15·5	16·0	18·9	7·6	8·7	9·2	7·8	11·4	12·8	7·4	8·9	11·7	11·3	12·2	13·4

Treatment A = microcrystalline sulphathiazole. Treatment B = ordinary sulphathiazole. Treatment C = lotio cupro-zincica.

days of impetiginous infection before admission, to allow statistically for variations in this period. But we found that the average stay in hospital was not much affected by the duration of infection before admission: hence the statistical analysis could be simplified by neglecting this factor.

We finally adopted two methods of comparing the three treatments. First we went through the cards and classified as failures all cases where the dermatologist in charge of the case noted that the patient failed to respond to the treatment, or that it had to be changed, or that the patient relapsed within 7 days (tables I and II).

TABLE II—COMPARISON OF TREATMENTS

Treatment	Failures	Successes	Total	Percentage of failures
Microcrystalline sulphathiazole	38	322	360	11
Ordinary sulphathiazole	38	347	385	10
Lotio cupro-zincica	61	312	373	16
Total	137	981	1118	12

The proportions of failures are not significantly different for the two sulphonamide treatments, but lotio cupro-zincica had a percentage of failures significantly higher than that of the sulphonamides. The clinical interpretation of the apparent inferiority of lotio cupro-zincica on the above test seems, however, far from certain. In part, at least, the proportion of failures as classified by us must reflect the doctor's confidence in the treatment rather than its actual therapeutic efficiency; for the less a doctor trusts a treatment the more readily will he abandon it for one in which he has more faith. Moreover, a third of the failures came from one hospital.

The failures include 19 cases where some degree of actual or suspected sulphonamide sensitisation appears to have developed owing to treatment with sulphathiazole, 7 of them with the microcrystalline and 12 with the ordinary form; but this difference is not statistically significant. As 745 cases were treated with sulphathiazole, the investigation suggests a risk of sensitisation in 2½% or, allowing for the possible effects of random sampling, from 1% to 4%.

A second and perhaps more satisfactory test was obtained from examination of the mean stay in each hospital of the men successfully treated. The average durations of stay in hospital of succcessful cases were:

Treated with microcrystalline sulphathiazole	11·3 days
Treated with ordinary sulphathiazole	12·2 ,,
Treated with lotio cupro-zincica	13·4 ,,

In eleven of the fourteen hospitals, treatment with ordinary sulphathiazole led to a longer stay than did microcrystalline, and in twelve of the hospitals treatment with lotio cupro-zincica led to a longer stay than did ordinary sulphathiazole. These differences give an average advantage of 0·84 days (with a standard error of 0·29 days) to treatment with microcrystalline as against ordinary sulphathiazole, and an average advantage of 1·20 days (with a standard error of 0·39 days) to treatment with ordinary sulphathiazole as against lotio cupro-zincica. The chances in favour of these two differences being significant are about 75 to 1 and over 100 to 1 respectively. In other words, after making due allowance for the possible random errors introduced by sampling, the investigation suggests that in successful cases treatment with 15% microcrystalline sulphathiazole leads to a mean stay in hospital up to 1½ days shorter than does treatment with 15% ordinary sulphathiazole; similarly, that ordinary sulphathiazole gives an average stay in hospital from ¼ to 2¼ days shorter than does treatment with lotio cupro-zincica in successful cases.

The 2% of patients who became sensitised to microcrystalline sulphathiazole in Bigger and Hodgson's trial agrees well with the 2½% met in the army trial. A therapy with a sensitisation risk of 2½% is not ideal for routine practice, and for general purposes the advantages of microcrystalline sulphathiazole in the treatment of impetigo contagiosa in adults are outweighed by disadvantages of difficulties of manufacture, shortage of supply, and other factors, including the introduction of penicillin as an alternative therapy. Nevertheless, for the specialist, Harris's introduction of this new form of sulphonamide to dermatology is of interest particularly as therapy with microcrystalline forms of sulphonamides may have a much wider application to skin-diseases of children than to those of adults.

CONCLUSIONS

Statistical analysis of the results obtained in 1118 uncomplicated cases of impetigo treated in three different ways suggests the following answers to the two questions which the investigation was designed to answer:

Treatment with 15% sulphathiazole administered in either form is significantly better than treatment with lotio cupro-zincica, except for the risk of sensitisation in 2½% of cases. The length of stay in hospital under treatment with either form of sulphathiazole is appreciably shorter than with lotio cupro-zincica.

As between the two forms of sulphathiazole, the advantage lies with the microcrystalline form, but this advantage, though probably significant, was outweighed in 1944 by scarcity of supply.

The statistical methods were arranged and carried out by Miss M. M. Johnstone, Major B. B. Swann, Capt. E. S. Cooper-Willis, and Sergt. A. J. H. Morrell. A report drafted by Capt. E. S. Cooper-Willis constitutes the main portion of this article.

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