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PRONTOSIL IN THE TREATMENT OF ERYSIPELAS

A CONTROLLED SERIES OF 312 CASES*

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There is by this time a considerable literature on the experimental and clinical results of the use of prontosil and the sulphonamide derivatives. It is not intended to review that literature in this paper. It may be pointed out, however, that so far as erysipelas is concerned no work has been published dealing with a large series of cases properly controlled. There has not been comparison with other cases of the disease during the same period of review, in every way similar as regards nursing and diet and differing solely in the special lines of treatment to be investigated. Such a series is presented here.

The material consists of all cases diagnosed as erysipelas after admission to Ruchill Hospital, Glasgow, from the middle of May, 1936, to the middle of February, 1937. Erysipelas is a notifiable disease, and Ruchill Hospital receives all notified cases of erysipelas admitted to hospital in Glasgow, so that the material is thoroughly representative of the incidence of the disease in this district during the period reviewed. All the patients were under the clinical control of one of us (T. A.).

Plan of Investigation

Apart from the specific treatment shortly to be described all cases were treated under strictly comparable conditions. Thus the wards to which they were admitted and the personnel of the nursing staff were common to all groups. A standard diet was adopted. When required the same laxatives were used. No local treatment was given. Ultra-violet light was chosen for the treatment of the control series because it was already the routine method employed in the hospital. There is a considerable literature indicating its value in the treatment of erysipelas. Publications by Fantus (1934), Titus (1934, 1934a), Sutherland and Day (1935), and Lavender and Goldman (1935) may be cited in evidence. The first 161 cases were, in order of admission, allocated to three special groups. Group 1 received treatment only by ultra-violet light; Group 2 only by prontosil; Group 3 both by ultra-violet light and by prontosil. The fatality rate when 161 cases had been admitted was exceptionally low, and as two-thirds of the series had received prontosil it was thought advisable to alter the proportion of cases treated with this drug. Therefore the second 151 cases were divided into three groups, of which the first two were the same as before, but the cases in the third group received treatment solely with Messrs. Burroughs Wellcome's concentrated scarlet fever antitoxin (globulin fraction).

* A Report to the Therapeutic Trials Committee of the Medical Research Council.

The numbers in each section vary slightly, since six cases were removed. In these it was considered, after further observation, that the original diagnosis of erysipelas was doubtful. Thus the actual numbers in the treatment groups are: ultra-violet light, 104; prontosil, 106; U.V.+ P., 54; antitoxin, 48. As the cases which received ultra-violet light or prontosil in the first series of 161 are strictly comparable to those similarly treated in the second group of 151, comparison is permissible between the cases receiving ultra-violet light and prontosil in the first series and those treated by scarlet fever antitoxin in the second group.

Details of Treatment

Ultra-violet Light.—A portable mercury-vapour lamp (Messrs. Kelvin, Bottomley, and Baird) was used at a distance of twelve inches from the margin of the lesion. For female cases the exposure was of eight minutes' duration, equal to one and a half erythema doses; for male cases the exposure was for ten minutes—in each case once daily. Exposures were repeated at intervals of twenty-four hours when considered necessary. The average number of exposures per case was 2.6.

Prontosil.—The original prontosil "red" of Messrs. Bayer Products, Ltd., was used. Treatment was begun on admission. The drug was given by mouth. The dosage was 1, 2, or 3 tablets of 0.3 gramme each at four-hourly intervals, and administration was continued until the temperature became normal, this being according to the original recommendation. The average case dosage was 5 grammes; the minimum dosage was 1.2 grammes, the maximum 15 grammes. Prontosil "soluble" was given by the intramuscular route in ten cases. In four it was the only method of employing the drug—the average quantity given being 1.5 grammes. In the other six prontosil "red" was also given by mouth. In these six cases the average dosage of prontosil "soluble" was 1 gramme in all. Cyanosis occurred in two cases. It was the only toxic effect present in this series. It was not severe, was only of short duration, and did not prevent the resumption of the drug. No saline purgatives or sulphur were used in any of the 312 cases.

Ultra-violet Light plus Prontosil.—This was a combination of the methods of treatment just described.

Scarlet Fever Antitoxin. One dose was given on admission, either by the intravenous or by the intramuscular route. A further injection was given in a few cases only.

The average dosage was 30 c.cm., equal to 30,000 units. All the patients were desensitized before the antitoxin was administered.

Records of Results

The following data were noted in each case: sex, age, duration of illness before admission, and whether the disease was primary or recurrent, idiopathic, or traumatic. The local lesion was considered with regard to its site, extent, swelling, painfulness, and tenderness; the patient's temperature and pulse rate were recorded four-hourly; and toxaemia was estimated under the following headings —prostration, headache, state of tongue, insomnia, vomiting, abdominal distension, and delirium. The urine was examined daily. Intercurrent diseases or degenerations were described; complications, relapses, and recurrences were noted. Each case was reviewed daily. In short, a careful attempt was made to record similar observations on each case in a comparative manner.

Assessment of Results

1. The distribution of the individual cases in the different treatment groups must be considered in respect of certain factors known to influence the course of the disease. Those regarded of greatest importance are (*a*) the duration of the disease before admission to hospital; (*b*) the age of the patient; (*c*) the severity of the infection; (*d*) associated diseases. All that need be stated at present is that tables constructed to show the relation of these factors to the types of treatment indicate an even distribution. A statistician who has examined them is satisfied that there was no weighting of any one line of treatment by any of these factors.

2. The question when "cure" is achieved has to be determined. The fatality rate in erysipelas is so low that it cannot be used in a small series of cases to assess the value of a therapeutic measure. It has other disadvantages, to be mentioned later. There is no single clinical feature which can be regarded as a satisfactory criterion of recovery. Cases are seen where the lesion continues to spread after the temperature has become normal; and, again, it is not uncommon for the local lesion to cease spreading while the temperature is still elevated and the patient continues in a toxic condition. In order to arrive at a conclusion in this series of cases attention was paid to the following points from the commencement of treatment: (i) the duration in days of spread of the local lesion; (ii) the duration in days of the primary pyrexia; (iii) the time in days which elapsed until the patient was free from the toxic symptoms. It was felt that the information gained from these observations would allow a comparison to be made between the effects of different methods of treatment.

Results of Treatment

Reference to the second paragraph under the heading "Plan of Investigation" will show that the number of cases treated with either ultra-violet light or prontosil alone is approximately double that of cases treated with ultra-violet light plus prontosil or with scarlet fever antitoxin alone. This must be borne in mind when considering the following tables. In compiling these tables patients who died have been excluded. There were fifteen deaths, and therefore the total number of cases is reduced to 297. The reasons for the exclusion of fatal cases from the first three tables will be mentioned later.

TABLE I.—*Spread of Lesion*

Method of Treatment	0 Days	1 Day	2 Days	3 Days	4 Days	5 Days and Over	Total Cases
Ultra-violet light ..	32 (32.65)	26 (26.53)	17 (17.34)	11 (11.22)	5 (5.1)	7 (7.14)	98
Prontosil	48 (47.06)	36 (35.29)	16 (15.69)	1 (0.98)	1 (0.98)	0	102
U.V. light + prontosil	19 (35.85)	26 (49.06)	7 (13.21)	0	1 (1.89)	0	53
Antitoxin	14 (31.81)	7 (15.91)	10 (22.73)	9 (20.45)	4 (9.09)	0	44

The figures in parentheses are percentages.

Table I shows a slightly more favourable result as regards cessation of spread in those cases which received prontosil, either alone or in combination with ultra-violet light. Thus the proportion of cases which showed no spread in the lesion after the end of the first day are: ultra-violet light, 59 per cent.; prontosil, 82 per cent.; U.V.+ P., 85 per cent.; antitoxin, 48 per cent. After two days in hospital the lesion continued to spread in only 2 per cent. of all cases receiving prontosil, but with the other forms of treatment the lesion continued to spread in 25 per cent.

TABLE II.—*Duration of Primary Pyrexia*

Method of Treatment	Duration of Pyrexia in Days								Total Cases
	0	1	2	3	4	5	6	More than 6	
Ultra-violet light	9	16 (17.98)	27 (30.34)	12 (13.48)	11 (12.36)	4 (4.49)	9 (10.11)	10 (11.24)	98
Prontosil ..	10	37 (40.22)	33 (35.87)	14 (15.22)	2 (2.17)	5 (5.43)	0	1 (1.09)	102
U.V. light + prontosil	2	18 (35.29)	20 (39.22)	8 (15.69)	2 (3.92)	0	1 (1.96)	2 (3.92)	53
Antitoxin ..	4	10 (25)	4 (10)	2 (5)	7 (17.5)	5 (12.5)	6 (15)	6 (15)	44

The figures in parentheses are percentages given after deducting those cases which were apyrexial.

Table II shows a slightly more favourable result as regards duration of pyrexia in those cases which received prontosil either alone or in combination with ultra-violet light than in the others. Thus after deducting the cases which were apyrexial the percentages of those with no fever after forty-eight hours' treatment are: ultra-violet light, 49; prontosil, 76; U.V.+ P., 74.5; antitoxin, 35. Pyrexia continued for more than three days in only 8 per cent. of all cases receiving prontosil, but with the other forms of treatment the equivalent percentage was 41.

TABLE III.—*Duration of Toxaemia*

Method of Treatment	Duration of Toxaemia in Days								Total Cases
	0	1	2	3	4	5	6	More than 6	
Ultra-violet light	11	12 (13.79)	22 (25.29)	19 (21.84)	15 (17.24)	6 (6.9)	4 (4.59)	9 (10.34)	98
Prontosil ..	5	18 (18.56)	40 (41.24)	22 (22.68)	7 (7.22)	7 (7.22)	1 (1.03)	2 (2.06)	102
U.V. light + prontosil	3	11 (22)	18 (36)	8 (16)	6 (12)	3 (6)	2 (4)	2 (4)	53
Antitoxin ..	5	4 (10.26)	4 (10.26)	5 (12.82)	8 (20.51)	7 (17.95)	5 (12.82)	6 (15.38)	44

The figures in parentheses are percentages given after deducting those cases in which there was no toxaemia.

Table III shows a slightly more favourable outcome as regards duration of toxaemia in those cases which received prontosil either alone or in combination with ultra-violet light. Thus after deducting the cases with no assessable degree of toxaemia the percentages of those free from signs of toxaemia at the end of forty-eight hours' treatment were: ultra-violet light, 39; prontosil, 60; U.V. + P., 58; antitoxin, 16. After three days in hospital 21 per cent. of all cases receiving prontosil remained toxic; the equivalent percentage with the other forms of treatment was 39.

In the paragraph "Records of Results" the component elements investigated under the heading of toxaemia are given. While it is admitted that the precise duration of toxaemia is difficult to assess clinically, the observations were all made and recorded by the same individual. It is therefore considered that they have a certain comparative value.

Some further points now call for consideration.

Recurrence

Table IV shows the number of recurrences which took place in each treatment series. Deaths are not excluded from this table; accordingly the total is 312 cases.

TABLE IV.—*Recurrences*

Method of Treatment	Number of Recurrences	Total Cases
Ultra-violet light	12 (11.5%)	104
Prontosil	9 (8.5%)	106
U.V. light + protonsil	3 (5.5%)	54
Antitoxin	3 (6.3%)	48

No significant difference was found in this series that would point to the action of prontosil in preventing recurrences. It must be remembered, however, that treatment of all types was given during the acute stage only, and was not maintained after the subsidence of the local lesion and the cessation of fever and toxaemia. In a further series we are now undertaking instead of prontosil "red" a variety of the colourless sulphonamide is being used, and there will be a longer period of treatment with the drug in the hope of lessening the incidence of recurrence.

Complications

Table V shows the incidence of those septic complications directly attributable to infection with erysipelas. Among such conditions are abscess formation, septicaemia, thrombosis, and nephritis. Deaths are included in this table.

TABLE V.—*Cases Showing Complications*

Method of Treatment	Number of Cases showing Complications	Total Cases
Ultra-violet light	32 (30%)	104
Prontosil	23 (21%)	106
U.V. light + prontosil	14 (26%)	54
Antitoxin	20 (41.6%)	48

Although there is a lower complicated-case rate in the patients treated with prontosil, the percentage is higher where prontosil and ultra-violet light are used together. In the prontosil-treated groups, however, the combined incidence of complications is 23.1 per cent., in the other treatment groups the combined incidence of complications is 34.2 per cent. This difference is suggestive.

One type of complication deserves special mention. The incidence of nephritis in the four treatment groups is: ultra-violet light, seven cases; prontosil, *nil;* U.V. + P., one case; antitoxin, *nil.* It has been suggested that prontosil may have an irritant effect on the kidneys: this is not borne out by these figures.

The question of associated diseases—metabolic, degenerative, or infective—must also be considered. This factor is difficult to present succinctly, and is, on the whole, associated with the age groups. From an examination of the case records it is not thought to be of any importance in this series as regards the prolongation of the course of erysipelas, but it is of considerable importance with respect to the percentage of deaths.

Deaths

The number of deaths was fifteen out of 312, a percentage of 4.8. This is low if compared with the annual fatality rate given for Ruchill Hospital in the medical

TABLE VI.—*Details of Fatal Cases*

Sex and Age	Treatment	Amount of Therapeutic Agent administered	Complicating Diseases	Days in Hospital	Remarks
M. 50	Ultra-violet light	3 doses; 2nd, 3rd, and 4th days	Nil	4	Pyaemia and septic arthritis confirmed p.m. Blood culture, positive strep.
F. 74	,,	3 doses; 5th, 6th, and 7th days	Chronic myocarditis	2	Auricular fibrillation. No p.m.
F. 54	,,	3 doses; 3rd, 4th, and 5th days	Carcinoma of pharynx being treated with radium needles	3	No p.m.
M. 69	,,	3 doses; 4th, 5th, and 6th days	Chronic myocarditis	11	Bronchopneumonia and nephritis. No p.m.
M. 67	,,	3 doses; 2nd, 3rd, and 4th days	Cholecystectomy performed immediately before admission	33	Left hospital in dying condition. Abscess of scalp. Acute nephritis. Uraemia
M. 40	Initial U.V. light failed; given prontosil	3 doses U.V. light: 1.5 gm. prontosil	Alcoholism	15	P.m.: Haemorrhagic nephritis. Streptococcal empyema
M. 18/365	Prontosil	3.9 gm. given in 2 days	Penis incised before admission as ? cellulitis	19	Recurrence. Extreme toxaemia. Abscess of sacrum
M. 76	,,	4.8 gm.	Advanced epithelioma of ear	2	No. p.m.
F. 4/12	,,	2.7 gm. + 3.3 gm. + 0.125 gm. For 2nd and 3rd attacks	Nil	18	Had two recurrences. P.m.: Streptococcal meningitis
M. 80	,,	7.8 gm. given in 2 days	Nil	10	Cerebral thrombosis. No p.m.
F. 50	U.V. light and prontosil	2 doses and 80 c.cm.	Previously paralysed	19	P.m.: Cerebral thrombosis. Erysipelas quite subsided at time of death
F. 54	Antitoxin	50 c.cm. { 30 c.cm. IV. 20 c.cm. IM. }	Diabetes mellitus	2	No p.m.
F. 58	,,	30 c.cm. IV.	Diabetes mellitus	10	No p.m.
M. 50	,,	30 c.cm. IV.	Alcoholism	5	P.m.
M. 57	,,	30 c.cm. IM.	Chronic myocarditis	2	No p.m.

officer of health's annual returns. The percentages there for the past few years are: 1935, 7.5; 1934, 7.6; 1933, 9.3; 1932, 9.6; 1931, 7.7. These percentages include all patients classified in the hospital returns as cases of erysipelas, which represent two-thirds of all notified cases in Glasgow, amounting to about 670 admissions a year. A number of cases so classified have been omitted from the present series where there was doubt as to the clinical diagnosis. This makes the figures difficult to compare.

A point of general interest which has been noted in connexion with similar work conducted on other diseases may be mentioned—namely, that an investigation of this type is undoubtedly beneficial to the cases as a whole. The nursing and medical staff are keenly interested; observation is more acute and sustained; and complaints and complications are watched for and dealt with immediately.

The fifteen deaths are distributed as follows: ultra-violet light, six; prontosil, four; ultra-violet light and prontosil, one; antitoxin, four. These figures must be considered along with causes of death and the complicating diseases. Table VI gives the relevant information.

It is obvious that the cases which ended fatally ought not to be included in the tables concerned with the assessment of the results of treatment. Otherwise a patient who died on the second day in hospital would be shown to have ceased to exhibit spread of lesion, pyrexia, and toxaemia on the second day. It is apparent from these data that no definite conclusions can be drawn from the fatality rate as to the relative values of the different methods of treatment. Death is often determined by the combination of erysipelas and some other disease. Nevertheless in the series of 160 cases receiving prontosil alone or combined with ultra-violet light the fatality rate was 2.5 per cent., while in the 152 cases not receiving prontosil the fatality rate was 6.6 per cent.

Discussion

There is little to add to the comments already made on the data presented. We would emphasize the difficulties attendant on drawing conclusions from the treatment of a disease so variable in its severity as erysipelas. Among important variables difficult to assess are the virulence of the infection and the natural resistance of the patient. In this connexion the general bodily health of the patient and the presence or absence of associated conditions—metabolic, degenerative, or infective—are of consequence. A very large series indeed would be required before one could assert that all such factors were evenly distributed. The cases were arbitrarily grouped in grades of severity, termed mild, moderate, or severe; since mild and moderate grades of infection will tend to recover spontaneously, it was thought that more valuable information might be obtained by considering in detail the cases grouped under the heading "severe." The total number of such cases was, however, only forty-nine, spread over the four treatment groups. This number is too small to permit of any deductions being made from it alone, although the results are in favour of prontosil treatment.

We can state that in this series, so far as we can detect, no known factor is unduly preponderant in one group of cases, and the cases in the different groups seem to us reasonably comparable. Nevertheless, while it is desirable that the therapeutic trial of a new drug should be made on statistical evidence as far as possible, there is a place for the expression of a clinical opinion. In five of the cases originally entered in the prontosil groups the condition on admission was so severe that a fatal result would not have been unexpected. It was felt that prontosil definitely contributed to their recovery. One case which was originally in the ultra-violet group showed uncontrolled spread with high pyrexia for six days, and was in the typhoid state when it was decided to employ prontosil; the patient's recovery was completely unexpected. This case has been left in the ultra-violet light series and does not affect the percentages in the tables. Two further cases in the ultra-violet light series also received prontosil at a later date. These likewise do not affect the percentages.

The benefits due to prontosil in erysipelas are statistically assessable and are great enough to render the use of such drugs advisable in this disease until some better form of treatment is available, but the action cannot on the whole be termed dramatic.

Conclusions

1. A series of 312 cases of erysipelas was treated under controlled conditions with (*a*) ultra-violet light; (*b*) prontosil; (*c*) ultra-violet light and prontosil; or (*d*) scarlet fever antitoxin.

2. There was an even distribution of the individual cases in the treatment groups in respect of factors known to influence the course of the disease, such as (*a*) the duration of the disease before admission to hospital; (*b*) the age of the patient; (*c*) the severity of the infection; (*d*) associated diseases.

3. The average case dosage of prontosil was 5 grammes; the average duration of prontosil treatment was two days. Treatment was given during the acute stage only, and was not maintained after the subsidence of the local lesion and the cessation of fever and toxaemia.

4. The cumulative evidence indicates that those cases which received prontosil showed better results in respect of curtailment of (i) the duration of the spread of the local lesion; (ii) the duration of primary pyrexia; (iii) the duration of toxaemia.

This study was undertaken at the request of the Therapeutic Trials Committee of the Medical Research Council. We are indebted to Messrs. Bayer Products, Ltd., for the supplies of prontosil "red" and of prontosil "soluble." The χ^2 values and standard errors of the tables have been calculated by Dr. P. L. McKinlay, Medical Officer, Department of Health for Scotland. The statements made in the text are all borne out by the values found. We wish to express our thanks to him for his services. We are also indebted to Dr. W. M. Elliott, superintendent of the Ruchill Fever Hospital, for permission to carry out this investigation.

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The scientific exhibits at the Paris International Exhibition are grouped in the Grand Palais (Champs Elysees), which has been incorporated as part of the exhibition under the title "Palace of Discovery." Here exhibits from all parts of the world demonstrate scientific progress throughout the centuries. Sections are devoted to physics, chemistry, medicine, and surgery, and to each of these important contributions have been made by the Wellcome Historical Medical Museum. They include a collection of stethoscopes, showing the development of the instrument from the time of its invention to the present day, an exhibit showing the evolution of the clinical thermometer, and another illustrating the history of the transfusion of blood.