Summary

The ABO blood groups of 317 patients with ulcerative colitis have been compared with those of 12,820 blood donors of the Oxford Region. No significant difference was found to exist.

In 101 patients with ulcerative colitis the proportion of "non-secretors" was normal.

We are indebted to Mr. Peter Collins, of the Oxford Regional Blood Transfusion Service, for the information regarding blood donors.

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LEG ULCERS: ASSESSMENT OF RESPONSE TO CERTAIN TOPICAL MEDICAMENTS*

BY

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Leg ulcers are such a serious cause of disability that any application that might shorten invalidism merits a trial. The present series of patients with this complaint was collected over a period of 10 years, and the purpose was to demonstrate the rates of healing with different dressing under in-patient hospital conditions. Obvious difficulties in any such venture include the wide choice of remedies claimed to be effective, and the tendency to yield to the subjective element in judgment on the part of the observer and his colleagues. With regard to the former difficulty, no attempt was made to institute an exhaustive, planned, and controlled experiment, preference being given to whichever treatment was thought likely to be most beneficial, starting with tried favourites but including some new ones as well; those which seemed on clinical assessment to be unduly slow in promoting healing or to be harmful to the patients being promptly withdrawn. The resulting information thus comprises something approximating to a record of treatment which would normally have been carried out in our unit. Interest was focused mainly on overcoming the latter difficulty and seeking to formulate an objective test whereby regression rates could be compared numerically and our clinical impressions corroborated or refuted.

Method and Material

The method entailed measuring the ulcer area when treatment started and noting the time of healing—or, as in eight of the cases, measuring again at a later date

*Based on a demonstration arranged by the department of dermatology and presented by one of us (J.C.P.L.) at the Scientific Exhibition of the B.M.A./C.M.A. Joint Annual Scientific Meeting, Edinburgh, July, 1959.

—and comparing the average regression rates per day when various proprietary and other types of application were under investigation. At first direct measurements were made; then for greater accuracy the method practised by physiotherapists was used, tracings of ulcers being made on transparent paper. These tracings were placed on graph paper, the small squares were counted, and the area of the ulcers was calculated in square millimetres. The answer was divided by the number of days taken for the ulcers to heal. In the eight cases referred to above, the healed area was divided by the number of days elapsing between these measurements (termed "measured" rates). Thus the average healing or regression rate per day was obtained.

Of the 271 patients (88 males and 183 females) chosen as suitable for final assessment, 40 appeared more than once in the series, suffering from multiple ulcers on different preparations or from ulcers which recurred after varying intervals, sometimes several years. The ages of the patients ranged between 17 and 84 years. Of the ulcers, 96% were classified as gravitational or "varicose," 3% as ischaemic (hypertensive or arteriosclerotic), and 1% as trophic. The left leg was involved in 50%, the right in 40%, and both legs in 10% of cases. On the final assessment of cases there were 343 ulcers, 302 of which healed with treatment, 16 otherwise disposed of, and 25 did not respond. Total duration since development of ulceration varied from one month to 50 years, whereas immediate duration, or the length of time the particular ulcer under treatment had been present, extended from 10 days to 20 years.

All the patients in the series were recumbent for the greater part of their stay in hospital. The appropriate treatment for any concurrent or underlying complaint was given and the patient was referred to another unit for adjuvant therapy as this became necessary. Ischaemic and trophic ulcers required their special regimen, including warmth and rest in bed with the limb loosely bandaged or covered with a cage, followed by sympathetic block and sympathectomy if other methods failed (Anning, 1954). Patients with both these types of ulceration were treated recumbent, in the horizontal position; but for gravitational ulcers, which formed the majority, the foot of the bed was generally raised. When these gravitational ulcers healed the patients were encouraged to be ambulant, applying dusting powder only and wearing a crêpe bandage applied from the toes upwards to below the knee. Later a heavy-duty below-the-knee elastic stocking was supplied. Light centripetal massage with the foot elevated was carried out by the patient or by a relative or friend.

Results

The results of the investigation are recorded in Table I, where the medicaments under unit and grouped headings are arranged in order of rapidity of mean rates of healing recorded as sq. mm. per day. The percentage of ulcers healed has also been recorded, but this is not considered to be of great significance, because most ulcers not grossly infected will heal eventually on any non-irritant application provided the patient is recumbent.

In Table I the number of cases, number of ulcers, and the mean and range of healing rates are recorded under each heading. Under "remarks" we find the number of ulcers which failed to heal, those in which this could be attributed to sensitization to the medicament

TABLE I.—Analysis of Results

Material	No. of Cases	No. of Ulcers	% of Ulcers Healed	Mean Rates of Healing (sq. mm./Day)	Range of Healing Rates (sq. mm./Day)	Remarks
Eusol ..	59	71	95.6	61.4	1-513	4 not healed, 4 at O.P.D., 1 "measured"
Furacin ..	16	17	75.0	59.3	5-114	1 taken out*, 4 not healed (2 sensitized), 1 not healed
Simple pastes, etc.	18	21	95.2	52.2	1-479	1 not healed
Ichthyol cal. liniment	57	74	97.3	49.0	1-421	2 not healed, 1 at O.P.D.
Antiseptics ..	12	16	50.0	40.0	3-134	7 not healed, 2 at O.P.D., 1 "measured"
Petroleum jelly	7	9	66.7	35.3	16-57	1 not healed, 2 "measured"
Zinc peroxide	49	77	100.0	33.7	0.4-312	All healed
Antibiotics ..	9	10	70.0	31.3	5-57	3 not healed (1 sensitized)
"Gelfoam"	23	25	76.0	27.9	1-99	3 not healed, 3 "measured"
Triiodo-thyronine	14	15	100.0	22.0	1-57	All healed
Saline ..	7	8	87.5	20.0	1-46	1 "measured"
Total ..	271	343				

* The mean rate of healing would not have taken this high reading (914 sq. mm. per day) into account.

employed being included in parentheses. "Measured" ulcers are those which, as already explained, were measured at the beginning and end of treatment instead of waiting for healing or deterioration to take place. Their rates of healing tended to be faster, and so all eight of them were excluded from the series. The same applies to one case (marked * on Table I) in which the rate of healing was found to differ so much from the others in the same group that it was decided to disregard it in computing the mean and so prevent bias. Seven cases treated at the out-patient department were likewise eliminated from the series because of a low average healing rate.

It will be noted that the most effective applications were all simple, old-fashioned remedies with the exception of "furacin" (nitrofurazone; 5-nitro-2 furaldehyde semicarbazone), and this had to be withdrawn in 4 out of 17 ulcer cases, having caused a contact eruption in the immediately surrounding skin of two of them. One very rapid rate on treatment with furacin—914 sq. mm. per day—was the one which had to be excluded from the series because the mean rate of healing would not have taken this high reading into account. This allowed eusol (Edinburgh University Solution, *B.P.C.*, a solution of 1.25 g. of boric acid and 1.25 g. of chlorinated lime in water to 100% and containing not less than 0.25% of available chlorine) to achieve clear superiority over all the other applications as regards mean rate of healing. This solution was diluted 1:4 with water, and in this dilution proved non-irritant even when continued as a dressing twice daily over a long period. Initially it was employed as a cleansing agent, but later it became apparent that it possessed outstanding healing properties as well.

Of the other applications specified in Table I, ichthyol calamine liniment has the following formula:

Ichthyol	..	..	1%
Calamin. praep.	}	..	āā 4 dr. (15.5 g.)
Zinc. oxid.			
Ol. oliv.	}	..	āā 4 fl. oz. (113.6 ml.)
Aq. calcis			

Like the other dressings it was applied twice daily. Under the heading petroleum jelly are included "tulle

gras" and "jelonet." Zinc peroxide consisted of 20% of this substance triturated with water. "Gelfoam" powder—animal gelatin complex recommended by Milberg and Tolmach (1954) and by Sulzberger and Baer (1954-5)—and triiodothyronine ointment (a salve containing the ultimate effective form of thyroid gland) showed little superiority in healing rates over saline soaks. Gelfoam is, however, pleasant to use and was approved of by the patients because of its soothing effect, but it tended to form a dry, powdery crust which often became infected underneath, even when the powder was combined with an antibiotic. Triiodothyronine was thought to be beneficial in sclerosed and indolent ulcers, where it led to the formation of granulations. Ulcers allowed to continue on saline soaks, whether normal or hypertonic, for longer than an initial cleansing period were few because they proved on early appraisal to be relatively inactive as healing agents. Details of the composition of "simple pastes, etc.," "antiseptics," and "antibiotics," and the results obtained with each, are recorded in Table II.

TABLE II.—Details of Medicaments Recorded Under Group Headings

Medicament	Composition	No. of Ulcers	Mean and Unit Rates of Healing (sq. mm./Day)	Range of Healing Rates (sq. mm./Day)	Remarks
<i>Simple Pastes, etc.</i>					
Eosin ..	½% in P.Z.	1	479	—	Healed
Ichthyol ..	1% " "	2	70	29-111	"
Gentian violet and brilliant green	āā ½% in P.Z.	4	43	13-81	"
Salicylic acid	½% in Zn Cr	2	32	12-51	"
Balsam of Peru	10% Ung. Hg., nit. dil. 25% P.Z.	7	30	6-60	1 not healed
Eosin ..	½% aqueous	1	7	—	Healed
Boric acid	½% in zn. ox. and ol. oliv. āā pts. aeq.	2	2	1-2	"
Salicylic acid	½% in p.m.f.	1	2	—	"
Thovaline ..	Talc., kaolin, zn. ox., c.l.o.	1	2	—	"
<i>Antiseptics</i>					
"Brulidine"	Dibromopropamide isethionate	8	46	3-134	2 not healed, 1 "measured", 1 at O.P.D.
"Bradosol"	Beta-phenoxyethyl-dodecylammonium bromide	2	8	—	"
"Phenoxetol"	Phenoxyethanol	2	—	—	1 not healed, 1 at O.P.D.
"Viacutan"	1% silver dinaphthylmethane disulphonate	4	—	—	None healed
<i>Antibiotics</i>					
"Terramycin"	3% oxytetracycline	2	49	40-57	Healed
"Tyroderm"	Tyrosin	1	37	—	"
"Aureomycin"	3% chlortetracycline	1	34	—	"
"Polyfax"	Polymyxin B sulphate and bacitracin	2	30	—	1 not healed
"Chloromycetin"	1% chloramphenicol	2	16	—	1 " " "
	3% " "	2	5	—	1 " " " (sensitized)

Under simple pastes, etc., the one outstanding healing agent was ½% eosin in zinc paste. Very much less efficacious were 1% ichthyol in zinc paste, ½% salicylic acid in zinc cream, ½% each of gentian violet and brilliant green in zinc paste, and balsam of Peru paste. Among antiseptics, only "brulidine" (dibromopropamide isethionate) was outstanding, and this has been thoroughly established by our clinical experience, for it is the only member of this group which we have

continued to use. Antibiotics showed "terramycin" (oxytetracycline), "tyroderm" (tyrothricin), and "aureomycin" (chlortetracycline) fairly equal in effectiveness, but we have no great faith in any antibiotics either as cleansers or as healing agents, because when organismal sensitivity tests were carried out healing did not seem to depend on whether or not the appropriate antibiotic preparation was applied, suggesting that the organisms present in leg ulcers are of little importance in causing chronicity.

It may be profitable to consider also some results which have been eliminated from or not included in the Tables. In the seven ambulant patients treated at the out-patient clinic the progress of healing was not only very slow but deterioration was frequent; for example, one "measured" rate at the out-patient clinic exceeded *in expansion* our fastest average regression rate. Other results from "measured" rates on recumbent patients corresponded roughly with those on similar treatments applied to ulcers left until healing took place, except that the former tended to be higher than the latter, and that is why they were taken out of the series. A record "measured" rate of 2,500 sq. mm. per day was obtained with a very large shallow ulcer treated in the initial stages with normal saline soaks, demonstrating their potency as cleansing agents. Paired comparisons carried out on 14 cases with two or more ulcers on which mean healing rates were estimated gave results not widely dissimilar to those obtained for the same medicament and recorded in Table I. Nine ulcers on forms of treatment not used often enough for grouping were omitted from our final assessment. One of these, the only one on hydrocortisone, had a healing rate of only 2 sq. mm. per day. Three cases on the Bisgaard regimen showed a mean healing rate of 73.3 sq. mm. per day (range 8-176); three cases on occlusive dressing 23 sq. mm. per day (15-31); and two on "tryptar" (crystalline trypsin) and "varidase" (streptokinase-streptodornase) did not heal.

Illustrative Case

A woman aged 63 had suffered from gravitational ulcer of the left leg for a total of five years after an injury, healing and recurring, with an immediate duration of 18 months. She had suffered from "phlebitis" 12 years previously and had had two injections into varicose veins since then. She was obese—weight 12 st. 11 lb. (81.2 kg.)—and her blood-pressure was 210/100. Culture of a swab from her ulcer for organisms revealed *Proteus vulgaris* and *Staph. aureus* (coagulase-positive), sensitive to terramycin, streptomycin, and chloromycetin. She was treated by bed rest and put on a reduction diet. Normal saline soaks were applied for seven days, 3% terramycin cream for one day (withdrawn owing to contact dermatitis), ichthyol calamine liniment for six days, and eusol in 1:4 dilution in water as soaks twice daily for 48 days; during the last period of treatment, copper sulphate crystals were applied for one day to hypertrophic granulations. The area of the ulcer on admission was 3,000 sq. mm., the total healing-time was 62 days, and the mean rate of healing was 48 sq. mm. per day.

Discussion

It is not claimed that the method we are introducing is a reliable guide to the complete value as a healing agent of each product investigated, but merely that it supplies an objective test which takes into account rapidity of regression in relation to the ulcer area. Using this test, we are in a better position to assess accurately the effect of medicaments employed than in dealing with

before-and-after photographs or the results of simple paired comparisons. Moreover, it is a procedure which anyone can employ, being available to the general practitioner, the hospital specialist, or the physiotherapist. Observation of the process of healing on a series of ulcer tracings adds greatly to the interest of treatment for both patient and medical attendant, and some modification of the method of estimating the ulcer area might make this less tedious for the latter.

We have stated that percentages of ulcers healed were not regarded by us as of great significance; nevertheless, from these results, coupled with the mean regression rates, it may be assumed that it is some recommendation for the remedies zinc peroxide and triiodothyronine that ulcers could be left on them until healing had taken place. What makes eusol and the other simple applications outstanding is that they combine ease of application with speed, efficiency, and safety in use. The onset of a contact dermatitis with sensitization eczema such as occurred when using furacin in this series prolongs the stay of a patient in hospital and greatly increases his suffering. It must be avoided at all costs, and we can be sure of doing so only by employing simple methods. The Bisgaard regimen in its original form (Bisgaard, 1948), necessitating a prescribed routine of deep massage and the application of special dressings with elastic support while the patient remained ambulant, was found most helpful in some chronic resistant ulcers, but it was far too elaborate and time-consuming to be used in more than a few. This led to a modification of our own being adopted in this unit, as detailed above.

It might be objected that a subjective element persisted even in this new method of assessment, especially when the decision to abandon any form of treatment was not instigated by the onset of contact dermatitis attributed to the medicament or where there was no obvious deterioration in the condition of the ulcer. Similarly, it was difficult on occasion to decide which medicament should be held responsible for the ultimate healing of an ulcer and whether more than one should not be given the credit. For example, in addition to the use of preliminary cleansing agents already referred to, copper sulphate crystals were often employed to treat hypertrophic granulations. Hydrocortisone ointment, too, appeared to facilitate this process—the only useful purpose we found it to serve in treating leg ulcers. Credit, however, was usually given to the application which had been applied the longest, on which progress had been most favourable, and on which healing had taken place. In the majority of ulcers treated the extent of the ulcer was estimated on admission of the patient to hospital and immediately prior to starting therapy, and the same application was continued throughout.

In a few ulcers greater difficulty was experienced, as in the case described. In this case eusol was credited as the healing agent in spite of the fact that others had been applied. When the final change in treatment was made the ulcer had become infected, and, but for the action of eusol, the infection might have extended and lymphangitis supervened, with the time before healing greatly prolonged.

The wide divergence of the figures recorded in Table I under "range of healing rates" is another possible ground for objection, as reflecting unfavourably on the consistency of results obtained under each head. But is this really so surprising when so many other factors have to be considered in dealing with leg ulcers besides

the ulcers themselves? We maintain that the average rates of healing have significance, not least so because both the aggregated results from numerous cases in Table I and the less numerous ones in Tables I and II correspond closely to our clinical impression accumulated in treating leg ulcers over many years.

The need for further investigation on the subject of leg ulcers is clamant, and representatives from all branches of medicine must co-operate in this. Many problems remain, but Anning (1954) has stated that venous thrombosis is the commonest cause of failure of the muscle pump leading to leg ulceration, and it occurred in 74.85% of the patients in his series. 27.6% of the women in Anning's series suffered from post-partum thrombosis, and it was hoped that the advent of antibiotics and improved maternity care might cause leg ulcers from this factor to become a thing of the past.

A. M. Giles (1960, personal communication) states that the incidence of true deep venous thrombosis in post-partum cases is very much less than in pre-antibiotic times, but there are coming to the fore resistant organisms which may result in a return of the original incidence of this complaint. Therefore we cannot afford to be complacent. We hope that the introduction of this technique will act as a stimulus to further research in the treatment of leg ulcers and that its first fruits, our advocacy of a reversion to simple methods of treatment, may lead to more efficient but less expensive therapy and to a great reduction in unnecessary suffering.

Summary

A series of 271 cases of leg ulcers was submitted to area measurement and the speed of healing calculated in sq. mm. per day while various medicaments were being exhibited.

Eusol produced the fastest regression rate, and it was concluded that simple applications and procedures are best in treating leg ulcers.

It is a pleasure to acknowledge the assistance of the ward sisters and nursing staff. Dr. Alex. Berrie, of Glasgow University, advised on the statistics. Messrs. Glaxo Laboratories and Messrs. Upjohn of America forwarded generous supplies of triiodothyronine and of gelfoam respectively.

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London County Council has issued a small booklet, *Notes for Guidance of Child Guidance Clinics*, by J. Wilson Wheeler (Children's Officer), W. F. Houghton (Education Officer), and J. A. Scott (Medical Officer of Health and Principal School Medical Officer). The main services are discussed under the three headings of: (1) special education for children remaining in their homes; (2) provision for placing children away from their homes; and (3) recommendations made to the juvenile courts. The booklet includes the names, addresses, and telephone numbers of the district care organizers, the area children's officers, and the divisional medical officers in the London boroughs.

TABLE FOR ASCERTAINING WHETHER DIFFERENCES BETWEEN PERCENTAGES ARE STATISTICALLY SIGNIFICANT AT THE 1% LEVEL

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In a previous paper (Garside, 1958) a table was given to ascertain whether differences between percentages are significant at the 5% level. The accompanying table can be used to find whether such differences are significant at the 1% level. The method of use of the present table is identical with that of the previous table.

Yates's Correction for Continuity

It has been asked whether Yates's correction for continuity (see Hill, 1955) can be incorporated when using the previous table. This correction can be used with both tables. It is never wrong to use the correction, but its effect becomes small as the numbers involved become large. It should, however, be used if Pa or (100 - Pa), whichever is smaller, multiplied by Nb or (N - Nb), whichever is smaller, is less than 1,000. If this product is less than 500, then, as stated in the previous paper, a more accurate method of finding significance should be used (see Fisher and Yates, 1948). At first sight, 1,000 and 500 seem very large, but they are percentages and correspond to actual frequencies of only 10 and 5 respectively. Pa, Nb, and N are defined in the previous paper.

To apply Yates's correction using either table, the difference tested—that is, that between Pa and Pab/b—should be reduced by 100/2Nb. If this corrected difference (Dc) equals or exceeds the corresponding percentage tabulated in the previous table, the difference is significant at the 5% level, and if Dc equals or exceeds the corresponding percentage in the present table then the difference is significant at the 1% level. In using the tables 1/Nb has to be found anyway, so the correction is simple to apply.

It can easily be shown that Dc—that is, |Pa - Pab/b| - 100/2Nb—divided by its standard error—that is, $\sqrt{Pa(100 - Pa)(1/Nb - 1/N)}$ —equals the square root of chi squared corrected for continuity—that is,

$$\frac{N(|AD - BC| - 1/2N)^2}{(A + B)(A + C)(B + D)(C + D)}$$

where A, B, C, and D are the cell frequencies in a fourfold table. Thus using the tables with the correction gives precisely the same results as using the corrected chi-squared test. An example will illustrate this and make the procedure clear.

Suppose the following data relate to two factors or symptoms:

	Yes	No	Total
Yes	3	10	13
No	9	2	11
Total	12	12	24

Then Pa = 50%, N = 24, Nb = 13, and N - Nb = 11. Pa multiplied by (N - Nb) equals 550, and therefore Yates's correction should be applied. Now Pab/b