A relapse means either that treatment has been inadequate or that reinfection has occurred. No particular organisms appear to be responsible. Chronic otitis media is often the cause of a relapse. Frequent recurrences or lack of treatment lead to chronicity which, once established, is well-nigh impossible to cure.

Treatment

Brain (1942) stressed that "treatment should be governed by two important facts. The first is that our protection from external irritants and infections depends upon a dry and intact horny layer, and treatment should be designed to maintain it. . . . The second fact of therapeutic importance is that living cells are instantly damaged by water or by grossly hypotonic solutions, and this applies to the skin when the protective stratum corneum is missing, or its continuity is disrupted by exudation."

Treatment resolves itself into two approximately equal parts—the thorough cleansing from the meatus of all particles of discharge, and the application of lotions to the inflamed meatal walls. The mechanism of mopping has been described, and its importance cannot be too strongly emphasized. Drugs are applied to the infected skin on wicks of ribbon gauze or painted on by means of wool-tipped wire probes. The ribbon gauze wick must be inserted gently so that it maintains contact with the walls in the whole length of the meatus. It should be changed daily, and some authorities moisten the wick with the appropriate solution every 12 hours. Cotton-wool adheres to the raw skin surface and should never be used. The selected solution must be non-irritant and isotonic; it should not stain the meatal walls or leave a deposit thereon; it should not dry enough to cause pain on removal. Pastes and powders allow infection to spread under them.

An acute oedematous otitis externa must first have the oedema reduced to permit complete cleansing of the drum and the deep anterior recess. Then the inflamed epithelium must be healed and finally dried and hardened. The drugs used for reducing oedema are 20% sodium sulphate, 8% aluminium acetate, or 10% ichthyol in hypertonic saline. The first two both tend to dry off during the course of 24 hours and are thus painful to remove. The ichthyol preparation has been used by me for nearly three years, and has proved most efficacious. After 48 hours' treatment the case usually resembles one in the exudative stage.

In this stage numerous solutions may be used to heal the skin. Those already mentioned may be persevered with, or one may try 10% ichthyol in water, 10% ichthyol in glycerin, 5% lead acetate, 10% argyrol, or calamine lotion. Of these, ichthyol in water dries quickly and is painful to remove; calamine lotion leaves a deposit on the skin which obscures the view of the progress; lead acetate has the same fault to a lesser degree, but has considerable healing properties, and is, in my experience, more efficacious than argyrol, which is superior for inflamed mucous membranes. Ichthyol in glycerin is probably the best all-round treatment, being soothing and easy to insert and remove.

When no further exudation is found the case resembles one in the congestive phase. Here a paint of 1% silver nitrate or 1% alcoholic solution of gentian violet should be used to harden the meatal skin. The latter solution stains the meatal skin and should not be employed until all discharge has stopped. It is the best treatment for fungous infection and for the granular type. When pus is green, or if *Ps. pyocyanea* predominates without green pus, 1% acetic acid, or a mixture of 1% acetic acid and 10% ichthyol, will give good results, although some patients find them uncomfortable, and they tend to dry off.

Pain is best treated with heat—fomentations, kaolin poultices, or hot-water bottles—and sedatives. The patient under treatment should be instructed not to scratch the ear, however itchy, and not to let water enter the meatus during washing. He should be told specifically not to use cotton-wool as a plug while the ear is discharging, as this only increases skin infection. Sea-bathing is forbidden for several months.

If a dermatitis of the auricle is present, good results are obtained with 1% ammoniated mercury in Lassar's paste applied on spreads and moulded to the pinna. Five per cent. sulphathiazole paste was efficacious, but was discontinued when it

was found to produce local reactions and even generalized sensitivity to light.

The question of chemotherapy in otitis externa is a vexed one. Many patients had had a course of one of the sulphonamide drugs before reaching hospital, with no benefit to the local condition. One has seen cases in which penicillin has been given parenterally for wound infections, furunculosis, or the aural condition itself, and yet otitis externa persists. The reason is obvious. Otitis externa is a mixed infection, and most of the causal organisms are insensitive to penicillin and the sulphonamides.

Syringing the ear in a case of otitis externa is always liable to increase the infection; but it is necessary sometimes when the secretion in the anterior meatal recess is too hard for mopping. To leave this debris is to invite recurrence. I have been in the habit of syringing these cases on the first day on which the ear is dry, and treating with ichthyol in hypertonic saline or ichthyol in glycerin for a day or two before going on to the paint.

It is with pleasure that I record my thanks to Col. C. H. K. Smith, O.B.E., M.C., commanding officer of a general hospital, for permission to publish this article.

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PENICILLIN GROWN FROM A NUTRIENT MEDIUM PREPARED FROM POTATO EXTRACT

BY

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The production of penicillin is rapidly growing. This is likely to continue for some time to come. Other antibiotics in application to agriculture, horticulture, and veterinary surgery will soon have to be produced on a large scale, possibly on a scale exceeding the production of penicillin. Under these circumstances the question of preparation of nutrient media becomes of great importance.

Conditions for growing moulds, to obtain the needed product of their metabolism, vary with the mould one is dealing with. To a large extent the result depends on the nutrient medium used. This medium must be both satisfactory and cheap. With very few exceptions the composition of such media is kept secret. In making known the composition and mode of preparation of a nutrient medium used by me I cannot claim to get a higher content of penicillin in the metabolic solution than that obtained in some of the media already used. I can only say that the titre of penicillin compares favourably with that obtained by using Czapek-Dox medium with the addition of yeast or corn-steep liquor, or by using the medium introduced by Challinor and McNaughton. The preparation of the medium is as follows:

Method

Potatoes or potato peelings are hydrolysed in twice the quantity of tap-water with 2% of HCl on the weight of potatoes. The hydrolysis proceeds for 2½ hours at a pressure of 3 atmospheres. After filtering the hydrolysate through a linen cloth an extract is obtained with an average glucose content of 5.5%. The sugar content naturally varies with the starch content of the potatoes or potato peelings used. In the case of potato peelings, unless they are used soon after peeling, a longer time is needed for hydrolysis. In the case of potatoes, these are washed and cut into pieces of approximately 1/2 to 2 cm. thickness. The necessity for cutting is avoided by using potato peelings.

The quantity of extract thus obtained from 1 kg. of potatoes with 2 litres of water and 20 c.cm. of strong HCl, after disposing of the solid residue by wringing out the linen bag used for filtering, is approximately 2,450 c.cm. This extract is diluted to 4% glucose content. We thus obtain 3,360 c.cm. approximately. The pH is roughly adjusted to neutral to litmus. Corn-steep liquor is added, 370 c.cm.—that is, 10% of the total quantity of medium. NaNO₃ is added—3% per litre; and activated charcoal—1/2% on weight of potatoes. The pH is adjusted to 6, and the medium sterilized

in the autoclave for a time, depending on the bulk of medium in preparation. While it is sufficient to have a litre flask containing 200 c.cm. of medium for 10 minutes at 1 atmosphere, a 5-litre aspiration bottle filled with medium requires three-quarters of an hour at 1 atmosphere pressure. It is advisable to add to the medium 10% of water to allow for evaporation in the autoclave.

This medium, when ready, is of a dark-brown colour. The addition of 1/2% of activated charcoal clarifies it to a certain extent. Fortunately, the waste water, after extraction of penicillin with amyl acetate, retains the bulk of the pigment, so that ultimately a powder is obtained with a degree of freedom from pigment corresponding to the stage of purification. Nor are these pigments, or other impurities derived from the medium, toxic: 1/2 c.cm. of sodium salt of 2,500 units per c.cm. injected into three mice did not seem to affect them adversely.

The titre of the crude penicillin solution obtained by using this medium, tested by serial dilution or ring method, frequently exceeds 60 units per c.cm. The average titre is above 30 units per c.cm. The highest figures obtained by me when using the Challinor and McNaughton medium were in the neighbourhood of 25 units per c.cm. I did not get up to this level with the Czapek-Dox medium.

Discussion

Apparently a nutrient medium prepared in the way described, besides containing all the glucose and most of the nitrogenous foodstuffs needed by a growing mould, must contain certain activating substances. By chemical analysis the nutrient medium was found to contain all the inorganic salts entering into the composition of Czapek-Dox salts except $MgSO_4$ and $NaNO_3$. The addition of $MgSO_4$ was shown by comparative experiments to be unnecessary, while $NaNO_3$ definitely improved the titre of penicillin. Corn-steep liquor certainly has a beneficial effect. In comparative experiments, while a flask containing hydrolysed potato medium would show at its height a titre of 15–20 units per c.cm., a flask containing medium to which corn-steep liquor has been added would show 60 and up to 80 units per c.cm. Before sterilization the addition of a small percentage of pulp, made from cabbage, or particularly carrots, seems to have a beneficial effect. As the height of titre constantly varies from day to day, and from experiment to experiment, I have not yet been able to draw definite conclusions as to the effect of such additions.

I need not enter into details of the actual cost of my medium. The economy is obvious—always on condition that the titre should not be lower than that of the other media used, and it does not seem to be so.

At present I have three experimental vessels—apparatus for penicillin production by surface growth in a continuous process—working at Highgate Hospital laboratory. From the seventh day—that is, from the time of the titre approaching its height—the average titre of all three tanks is 34.5 units per c.cm. What is the cost of this medium per litre? It amounts to the cost of 100 c.cm. of corn-steep liquor, 3 g. $NaNO_3$, 1 g. activated charcoal, and the potato peelings, which I get either from a hospital kitchen or from any canteen in the neighbourhood—free of charge. Working on a large scale, the additional cost would be the transport of potato peelings or diseased potatoes to the factory. True, on a farm one may use the peelings for feeding pigs, but the market value of it would hardly exceed 10s. a ton. One must therefore expect that agricultural waste will ultimately play an important part in the preparation of media for the production of various antibiotics.

I am much indebted to Dr. J. M. Alston for his constant interest and help in my work on antibiotics, and I must thank the London County Council and Dr. J. R. Reed for enabling me to work at Highgate Hospital.

The Federation of the British Legion has approved a recommendation of the Council of Management of the British Legion Village for the appointment of 21 medical men as honorary consultants to Preston Hall, Maidstone, Kent; the British Legion Sanatorium, Nayland, Colchester, Essex; and Douglas House, Bournemouth, the convalescent seaside annexe of Preston Hall. During the absence of Dr. J. B. McDougall (medical director of the British Legion Village), who is now attached to U.N.R.R.A., Dr. Frederick Heaf has been appointed honorary consulting medical director. The consultants will form a medical committee under the chairmanship of the honorary consulting medical director to advise the Council of Management in all medical matters connected with the British Legion Village.

HYPERSENSITIVITY TO TRANSFUSED BLOOD

BY

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A patient who is believed to be suffering from the rare disease called lupus erythematosus diffusus required a series of transfusions on account of persistent anaemia. As a result of these transfusions a remarkable succession of antibodies has appeared in her serum. The patient's red cells are Group O, M, P, Rh₁Rh₂, and negative with the three "new" antibodies to be described. She has never been pregnant.

Transfusions

Date	Donor's Name	Donors' Groups			
		Rh	Anti-Lutheran	Anti-Willis	Anti-Levay
1 Feb. 2, 1944	Marshall	Rh ₁ rh	—	—	—
2 Aug. 19, 1944	R. B.	rh rh	—	Unknown	—
3 Aug. 19, 1944	Lutheran	rh rh	+	—	—
4 Sept. 23, 1944	Willis	Rh ₁ Rh ₂	—	+	—
5 Sept. 29, 1944	Mules	Rh ₁ rh	—	—	—
6 Oct. 6, 1944	Howes	Rh ₁ Rh ₂	—	+	—
7 Nov. 7, 1944	Levay	Rh ₁ Rh ₂	—	—	+
8 Nov. 20, 1944	Allington	Rh ₁ Rh ₂	—	—	—
9 Jan. 31, 1945	"	Rh ₁ Rh ₂	—	—	—

Anti-Lutheran = The patient's serum taken at the end of Aug., 1944.

Anti-Willis = The patient's serum taken in Oct., 1944.

Anti-Levay = The patient's serum taken in Nov., 1944.

A specimen of serum taken shortly after the Lutheran transfusion was found to contain the rh agglutinin called St (γ Fisher); the "incomplete" form of this antibody was also present. More interesting, however, was the finding of another separable agglutinin, called anti-Lutheran in the table. The red cells of 8–9% of the English population, irrespective of the ABO, MN, P, or Rh groups, are agglutinated by this antibody. The Lutheran antigen is inherited as a dominant Mendelian character. The statistical and family evidence will be presented in detail elsewhere.

The St and anti-Lutheran antibodies gradually disappeared, their titre being low at the time of the September and October transfusions. After the Willis, Mules, and Howes transfusions a second "new" antibody—anti-Willis—appeared. The donor Howes's blood presumably assisted in this immunization, for Howes also has the Willis antigen. The Willis antigen is inherited as a dominant Mendelian character independent of ABO, MN, or P but not independent of Rh, and it is now practically certain that it is controlled by another allele at Fisher's C-c locus (Race, 1944), which may be called C^w. The Willis antigen is present in about 7% of Rh₁Rh₂ bloods, and the relative frequencies of the three alleles in the English population must be about C 43.5%, C^w 1.5%, and c 55%. Again the evidence for this interpretation will be presented elsewhere.

After some weeks of existence anti-Willis faded from the patient's serum, but towards the end of this period Levay's blood was given. This blood also proved to be incompatible, for about 14 days later a weak agglutinin—anti-Levay—was evident. The Levay antigen is a rare one and probably also a "dominant," for so far it has been found only in the blood of Levay and in the blood of this donor's father, but not in several hundred random bloods examined. All three "new" antibodies are more active at 37° C. than at lower temperatures.

Attempts to immunize one volunteer to the Lutheran antigen and two to the Willis have so far had no success. As the Lutheran and Willis antibodies may not be reproducible, and as the supply of antiserum is limited, it is proposed to deposit the names and addresses of as many of the Lutheran and Willis positives as are willing to help at the Bureau of Human Heredity, 115, Gower Street, London, W.C.1. It is hoped with the help of Major Moloney, of the U.S. Army Medical Corps, to make some equivalent arrangement with people whose homes