aborting. Hence the incidence of post-abortion sensitisation probably cannot be eliminated. Nevertheless, much can be done to reduce the number of cases appreciably. Surprisingly, many doctors are still unaware that anti-D immunoglobulin should be administered in these cases. Occasionally it is difficult to pinpoint the time of the abortion. Samson and Mollison,⁵ however, found that administering anti-D immunoglobulin up to 13 days after an injection of Rh-positive cells was effective in preventing sensitisation. Anti-D immunoglobulin should be given even at this late stage after a possible abortion. Roughly 20 cases a year of post-abortion or administrative failures of protection occur in the Yorkshire region—that is, a third of all new cases. If this region is typical eliminating these cases would greatly reduce the total incidence in Great Britain.

Primigravidae who are sensitised before anti-D immunoglobulin is normally administered make up most cases of so-called failures of protection. Several centres have instituted a programme of antenatal administration of anti-D immunoglobulin, which is also being actively considered in Great Britain. Regimens vary from one dose, usually at 28 weeks, as in the Hamilton (Canada) series and a Swedish series, to a two-dose regimen usually at 28 and 34 weeks in an Australian programme and the Manitoba project (unpublished data). Preliminary results suggest that antenatal administration of anti-D immunoglobulin reduces the incidence of antibodies detected at six months after delivery, but it is too early to be certain that it reduces the number of sensitised mothers in subsequent pregnancies. If it is shown that antenatal injection does reduce the incidence of sensitisation the incidence in the Yorkshire region would decrease by 20 to 30 cases a year. If this again is typical it would mean a decrease of 300-400 cases a year in Great Britain. Nevertheless, it would entail administering three times as much anti-D immunoglobulin as at present, a costly enterprise. Moreover, the number of new cases might be similarly reduced

by administering anti-D immunoglobulin after *all* Rh-negative deliveries and after every abortion.

One of our findings is of theoretical as well as practical interest. The fall in the incidence of Rh antibodies in Rh-negative women was 70%; the fall in the incidence of Rh-positive mothers with antibodies was 19%, which presumably reflects the fall in the number of women having babies. Nevertheless, the fall in the number of Rh-negative women with non-Rh antibodies was 35%. This suggests that anti-D immunoglobulin may have a non-specific effect, and supports the thesis of Woodrow and others in Liverpool⁶ that the mechanism of anti-D immunoglobulin protection is not antigen-specific. More data on this topic are needed.

We thank all obstetricians in the region for their help and co-operation, and for willingly making available the notes of the patients concerned; and the clerical staff for patiently obtaining the information required.

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Today's Treatment

Use of antibiotics

Antifungals

R Y CARTWRIGHT

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An increasing number of specific antifungal agents are now available for treating patients with fungal infections. It is important that these drugs are used wisely to reduce the emergence of resistant strains—a familiar problem with antibacterial agents. Many of the new antifungals are suitable for treating both superficial and deep mycoses. The management of a patient with a fungal infection, however, may not depend on specific antifungals, as the infections, especially those that are deep seated, may be secondary to another disease. Failure to recognise and control the underlying factors may result in the apparent failure of an antifungal agent. Another cause of

failure to control many deep-seated mycoses is that they are not diagnosed early in the disease. Not only should underlying factors be considered in fungal diseases but in patients with recognised predisposing factors the possibility of a fungal infection must be remembered.

The diagnosis of a fungal infection should whenever possible be established by microscopy, culture, or serology before treatment starts. I cannot consider all antifungals in detail in this article, but I will discuss the main groups of antifungal drugs and their application to treating the commoner fungal infections in Britain.

Griseofulvin

Griseofulvin (Fulcin, Grisovin) is a unique antimicrobial agent that is absorbed from the gastrointestinal tract and is then selectively concentrated in a single tissue—keratin—where it

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reaches an active concentration. It inhibits dermatophytes but not yeasts or other fungi. Naturally occurring resistant strains of dermatophytes have not been described, and resistance does not develop during treatment. The inhibition is due to interference with the polymerisation of microtubule protein into microtubules, this action being "static" as opposed to "cidal." Cure of the lesion depends on the growth of new keratin and the shedding of infected layers, a process that may take weeks or months. Griseofulvin is inactive when applied topically. Absorption from the gut is related to the particle size of griseofulvin—smaller particles being absorbed best.

INDICATIONS

Griseofulvin is indicated in dermatophyte infections that cannot be treated with topical compounds, have failed to respond to topical treatment, or are deep seated. It is most effective in skin as opposed to nail infections.

PRECAUTIONS

Griseofulvin increases the effect of alcohol and diminishes that of anticoagulants. Barbiturates diminish the effect of griseofulvin and should not be given at the same time. Griseofulvin should not be given to patients with porphyria or severe liver disease. Side effects may include headache, nausea, and vomiting.

ADMINISTRATION

Adults should take 500-1000 mg daily either as a single dose or two equal doses. Children should take 10 mg/kg body weight/24 hours. Doses should be taken after meals to enhance absorption.

DURATION OF TREATMENT

Skin and hair infections require 4-6 weeks' and nail infections up to 12 months' treatment.

Polyenes

The introduction of the polyene antifungal agents in the 1950s was a major advance in treating fungal infections. Nystatin (Nystan), candicidin (Candeptin), hamycin, and natamycin (Pimaricin) have similar properties and are all administered topically—mainly to treat candida infections. Amphotericin B (Fungilin) is the only polyene also available for parenteral administration. It has a broad antifungal spectrum and despite its toxicity remains the most important drug in managing systemic mycoses.

TOPICAL PREPARATIONS

Nystatin is the most frequently prescribed topical polyene, although there is no evidence of the superiority of any one topical polyene. Its principle value is against vaginal candidiasis. Taken by mouth it reduces the fungal and yeast content of the gut and is not absorbed, even in patients with ulcerative bowel conditions. Pulmonary infections have been treated by aerosol inhalations and the injection of nystatin paste into mycetoma cavities. Resistant strains of fungi and yeasts are not encountered in clinical practice. All the topical polyenes are virtually free of both toxic and allergic side effects.

INDICATIONS AND ADMINISTRATION

Vaginal candidiasis usually responds well to nystatin, one pessary being inserted high into the vagina for 14 consecutive

nights. The sexual partner should apply nystatin cream to the glans penis for the same period. There is no need to abstain from intercourse. If the condition recurs the woman should be advised to insert two pessaries night and morning for six weeks. The couple should also be given oral nystatin, 500 000 units eight-hourly, for ten days.

Oropharyngeal candidiasis—One amphotericin B lozenge (10 mg) should be sucked every four hours. In severe cases 1 ml of a suspension containing 100 mg/ml should be used. The lozenge or suspension should be retained in the mouth for as long as possible.

Ocular candidiasis—Nystatin as a 3.3% ointment or a 5% suspension of pimarinic acid should be used but they are effective only for superficial infections affecting the conjunctiva.

Otitis externa due to yeasts and fungi has been successfully treated with an insufflation of nystatin either in boric acid or lactose.

PARENTERAL AMPHOTERICIN B

As a dispersible colloid complex with sodium desoxycholate amphotericin B can be administered parenterally, and, although usually given intravenously, it can also be injected into the cerebrospinal fluid, joints, and the peritoneal cavity. The site of administration should, if possible, always be related to the site of infection, as over 90% of amphotericin B is bound to serum proteins, and it passes poorly from the blood to other body fluids. Only a small fraction passes into the urine or sputum.

Treatment with amphotericin B is often controlled by the toxicity and side effects of the drug. The main toxic effects occur in the kidneys and may include decreased glomerular filtration rate, renal arteriolar vasoconstriction, tubular degeneration, nephrocalcinosis, decreased concentrating ability, hypokalaemia, renal potassium wasting, and renal tubular acidosis. Fortunately most of the lesions are reversible if detected early and the amphotericin B stopped, although the glomerular filtration rate may be permanently reduced. It has been suggested that the nephrotoxic effects can be reduced by the concomitant administration of intravenous mannitol. Reactions during an amphotericin B infusion are frequent, varying from mild fever and nausea to high temperatures, rigors, vomiting, hypotension, and delirium. These reactions may occur even with a 1 mg test dose infused over 20-30 minutes. Their severity may be reduced by phenothiazines and hydrocortisone. Local thrombophlebitis is a further complication; only dilute solutions should be used with scalp vein needles, and the infusion site should be changed for each dose.

Despite all these toxic effects and reactions amphotericin B remains the prime drug in managing systemic mycoses and if used early and correctly is life saving. Fear of the drug should not prevent its use but should ensure that its use is correctly monitored and the dosage adjusted accordingly. The following should be undertaken twice weekly: creatinine clearance, plasma electrolyte, pH, and bicarbonate estimations; full blood count; and electrocardiography. There is now increasing evidence that if amphotericin B is combined with flucytosine or rifampicin the effective dose can be reduced.

Parenteral amphotericin B should be prepared and administered in accordance with the manufacturer's instructions. An alternate daily regimen is therapeutically satisfactory and may be given on an outpatient basis, although the patient should be in hospital for the first two to three weeks of treatment. Treatment may be necessary for many weeks, especially in patients with fungal endocarditis or meningitis.

FLUCYTOSINE

Flucytosine is a synthetic antifungal drug that has been used successfully in treating patients with systemic candidiasis, cryptococcosis, and toruloposis. It may be given intravenously, although this is seldom necessary as it is well absorbed from the

Scheme for choosing an antifungal drug in a patient with systemic mycosis.¹

gastrointestinal tract. Less than 5% is protein bound, and it is rapidly distributed through the body fluids. Therapeutic concentrations are obtained in the cerebrospinal fluid after ingestion. It can be used in combination with amphotericin B, and against some yeasts a synergistic effect may be obtained.

Unfortunately not all strains of yeasts are sensitive to flucytosine, up to 15% of fresh isolates of *Candida albicans* being resistant. Resistance may also develop during treatment, and it is essential to test all strains isolated before and during treatment. Combination treatment with amphotericin B may reduce the emergence of resistant strains and should be used in severe yeast infections. Flucytosine should not be used topically; there are satisfactory alternatives, and the drug should be reserved for systemic infections.

Flucytosine is excreted unchanged through the kidneys, and if renal function is impaired the serum concentration may rise to a toxic level with subsequent marrow and liver depression. Flucytosine should not be given to patients receiving cytarabine hydrochloride as it is competitively inhibited.

INDICATIONS

Flucytosine is the drug of choice in patients with systemic yeast infections, provided the infecting strain is sensitive on in vitro testing. In severe infections such as candida endocarditis or cryptococcal meningitis it should be given in combination with amphotericin B.

ADMINISTRATION

In patients with normal renal function 50 mg/kg body weight should be given every six hours. If there is renal impairment the optimum dose to maintain serum concentrations between 25-100 mg/l should be determined for the individual patient by assaying the serum concentrations. A six-hourly dose schedule reduces the oscillations in serum concentrations. If the patient cannot take the drug by mouth it may be given in a 1% intravenous solution.

Imidazoles

Clotrimazole (Canesten) and miconazole nitrate (Daktarin, Gyno-Daktaris, and Monistat) are currently marketed in Britain, although there is a range of imidazole derivatives at

various stages of development. As a group the imidazoles have a broad antifungal spectrum including yeasts, dermatophytes, and filamentous fungi, although strains vary in their susceptibility to individual compounds. Resistance during treatment has been reported, but the incidence appears to be low.

Clotrimazole and miconazole are used mainly for topical treatment, although miconazole can be given both by mouth and intravenously. Absorption from the gastrointestinal tract produces low serum concentrations and is often associated with nausea and abdominal discomfort. Intravenous miconazole is formulated with polyethoxylated castor oil, lactic acid, methylparaben, and propylparaben. Local venous irritation may occur, and a small needle and a different site should be used for each infusion.

INDICATIONS AND ADMINISTRATION

Vaginal candidiasis responds well to both clotrimazole and miconazole. A six-day course of clotrimazole pessaries is recommended and a ten-day course of miconazole cream. Sexual partners should be given the corresponding cream to apply to the glans penis. Recurrent cases respond well to a 28-day course of clotrimazole pessaries. The treatment should continue through menstruation. Occasionally it may be necessary to give two consecutive courses.

Dermatophytosis—A 1% miconazole or clotrimazole cream should be applied to the infected skin, and treatment should continue until the lesion has cleared. Formulations with a steroid are available and may be valuable in initially reducing the inflammation. They should not be used unless dermatophytosis has been definitely diagnosed and then only until any inflammation has subsided.

Oropharyngeal candidiasis—Miconazole gel will bring rapid relief to patients with oropharyngeal candidiasis. The gel combines 2% miconazole base. The adult dose is 5-10 ml six-hourly.

Systemic mycoses—Intravenous miconazole should be considered in patients with a systemic mycosis that is not susceptible to flucytosine and who cannot tolerate amphotericin B. In the USA intravenous miconazole has been effective in some patients with systemic coccidioidomycosis. Econazole, which is under development, may be of more value than miconazole for systemic aspergillosis but not for candidiasis. Oral miconazole, 250 mg six-hourly, reduces the gut carriage of yeasts.

Tolnaftate

Tolnaftate (Tinaderm) was one of the first synthetic antifungal compounds used topically. Although it has a broad spectrum of activity against the dermatophytes, its use is primarily in the treatment of tinea pedis.

Pecilocin

Pecilocin (Variotin) is an effective antibiotic that can be used topically in patients with a dermatophyte infection.

Which antifungal?

Superficial mycoses—Dermatophytic infections can either be treated topically or with oral griseofulvin. The route will usually depend on the site and severity of the lesion and the ability of the patient to apply a cream or take tablets. The choice of a

topical antifungal is made mainly on the preference of the prescriber and the patient as there have been few comparative trials. Comparison with Whitfield's ointment have, however, shown the effectiveness of this inexpensive compound. Unfortunately many patients find an unacceptable irritation from Whitfield's ointment.

Acute vaginal candidiasis will respond well to polyenes and imidazoles, although the relapse rate may be lower with the latter.

Systemic mycoses—The drug of choice depends on the susceptibility of the infecting fungus, and the patient's renal function and ability to tolerate the drug. The figure gives a scheme that has been found useful in clinical practice.

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MATERIA NON MEDICA

Monks' city

As a student my idea of Heaven was Munich, rebuilt and without the American Army of Occupation. True, because of its role in the Nazi movement, some thought my choice of a favourite city curious, but one could point out that Munich had also housed one of the first workers' governments, after the 1919 revolution overthrowing the monarchy—and in any case would one debar Florence because of the Borgias, Madrid because of the Inquisition, or Oxford because of the Appeasers? Returning there after over 20 years, I wondered whether Munich would live up to youthful Schwärmerei or whether its relaxed Southern ways would not have been replaced by the frenetic heartlessness that now afflicts so many north German cities. I need not have worried: the easy-going quality that Thomas Mann loved is still there; the city retains a human scale which can best be enjoyed on foot; and the buildings have been restored so that few could appreciate the devastation present at the end of the war. Above all, there is so much to do that is free or cheap: stroll in the parks or by the Isar, listen to the orators on their soap-boxes, and see some of the finest baroque and rococo churches in existence.

Munich has taken advantage of having to rebuild so extensively by constructing a large underground system, which despite the presence of few staff is, like the rest of the city, noticeably free from litter and vandalism. Why the difference between this and the great cities in Britain? Could it be with everything so painstakingly rebuilt in the recent past that the local youth know that destruction is a negative and depressing business? Is vandalism in this country merely part of the national delight in grubbiness, which equates winning a Nobel Prize with two inches of dust covering the laboratory bench? Or could it be that Munich has not allowed the vandalism legally perpetrated by adults, notably in the form of the motor car and tower blocks defacing city centres? The pedestrianised centre of Munich permits only trams down its streets, which glide silently along on rubber tyres. And if any of the great musicians associated with the city—Richard Strauss, Wagner, Mozart, or even Orlando di Lasso—were to stand where the English Gardens are situated now they would find the skyline virtually the same as it was in their day—STEPHEN LOCK (London).

Miracle of modern electronics

There was an air of excitement in Liverpool's Philharmonic Hall. The rows were filling rapidly with the invited audience, the Philharmonic choir were taking their places on the platform, and the orchestra were filing into their seats. But it was not just an ordinary concert: this one was to be televised (or tele-recorded, to be more accurate, for transmission some time in the future). Thus the interior

of the hall looked very different from usual with an assortment of microphones everywhere—from the ceiling, on long stalks from the floor, and strewn around the platform. Extra lighting abounded, dazzling and hot. Scaffolding had grown up in unaccustomed places to accommodate large wide-ranging cameras on small platforms. The cameraman on the stage wore a dinner jacket. Outside stood the control van and five others, all proudly proclaiming "BBC TV" on their sides—in fact, the whole panoply of modern technical and electronic miracles.

A hush fell over the auditorium. The conductor walked in and we waited for him to introduce the first piece. But not yet. Sorry, says the director, we are having a little trouble with one of the cameras. And I could see in front of me that the picture on the small monitor attached to the camera in the front circle was varying in intensity. Three people frantically fiddled with all the knobs—to no avail. Suddenly one of the back-room boys rushed upstairs, took a look at the errant camera, and then banged it hard with his fist on the side—and all was well. We can start now, says the director, and up went the conductor's baton—MYER GOLDMAN (consultant radiologist, Liverpool).

Sunrise

The local had provided us with a French wine with a fancy label and a taste like gripe water. Predictably a raging thirst ensued and at 5 am I was forced downstairs for a drink. The water came from the beck and was ice cold, as were the kitchen flags. Through the cottage window I could see the valley bathed in moonlight. The sky was cloudless and it was clearly a morning to watch the sun rise.

For once, we had beaten the farmer to it, but the sheep were already up and about and surprised to see us. As we climbed Walna Scar the peaks of Scafell appeared, snowclad and glowing in the light of the full moon. In our haste to reach the summit we climbed the 2000 feet in under an hour, only to find an icy wind on top and little sign of dawn. In the darkness we searched for shelter and watched Blackpool twinkling in the distance. On the moor south of Walna Bronze Age remains have been found and my sympathy was cordially extended. What the boys did to keep warm on windy November nights must remain speculative. As dawn progressed we spotted a cosy shelter some 30 yards from the ditch in which we had been unsuccessfully shivering for the past hour. The stone shelter was warm and we blessed the labours of the visionary shepherd who made it. To keep warm we climbed Brown Pike and watched the clouds turn purple and crimson until finally the sun appeared over Conistone, and my camera shutter froze at the vital moment. Not by the clicking of a mere shutter are such glories to be recorded—P W BARRITT (SHO in obstetrics, Yeovil).