any rate, might well be an illusion based on statistical fallacies. I went on to point out that an increased discharge rate was an unreliable prognostic index. What was in fact happening was that a proportion of patients discharged with perhaps indecent haste from mental hospitals, not necessarily cured or even improved, were being redistributed in the community in a variety of ways, most of them socially retrogressive, before ultimately being returned to the mental hospital.

From what has been disclosed in this paper it would seem that one of the important centres of redistribution is the prison. A hospital bed is, in effect, being exchanged for a prison cell. Historically this situation is by no means new. Penrose (1949), for example, states "there is an inverse relationship between the number of beds provided for the mentally ill and defective and the number of people in prison." But to allow this trend to continue, or increase, as it appears to be doing, would be socially disastrous and morally indefensible.

As for "community care"—the currently popular psychiatric catchphrase—the question arises: Does the community care? The social failure of so many of the mentally ill offenders studied is in itself an index of the failure of the community to look after them. Seemingly, it is the case that the community, in London at least, is not overzealous in its efforts to look after the chronic psychotic in its midst.

The danger inherent in a tepid welcome-on-the-mat for the mentally ill is that if they continue to be funnelled into the community from the mental hospitals without adequate provision, then even those doors now open to them may be slammed in their faces. The point is excellently made by Jones and Sidebotham (1962). They say, "If public tolerance is to be maintained in this country it is important that we should not try it too severely, and that we should proceed with care in releasing those whose actions might constitute a danger or an offence to the ordinary citizen"—with which statement, on the evidence supplied, I heartily concur.

Summary

In 1961, the first full year after the implementation of the Mental Health Act, 1959, there were 98 male offenders admitted to Horton Hospital, Epsom, whose catchment area is in Metropolitan London. In 1959, the last full year before the Act, the corresponding number was only 19. The paper sets out the results of an inquiry into this fivefold increase in the number of offenders in 1961.

In 1961 79 (81%) of those admitted were suffering from schizophrenia, the characteristics of which are reflected in all facets of the inquiry.

In 63 (66%) offenders, 56 of whom were schizophrenics, there was documentary evidence of previous mental illness. Forty-one had had multiple admissions to hospitals and 47 had each spent an aggregate of more than six months in them. It was a fair assumption, therefore, that a high proportion of the offenders were in fact chronic psychotics—that is, in all probability chronic schizophrenics. This must account in some measure for their social failure, evidence of which lay in the commission of antisocial acts.

Fifty-three of those admitted had committed their offences within two years of the last recorded discharge from a mental hospital. The conclusion must be drawn that the major source of the steep increase in the number of offenders is the mental hospitals themselves.

The grave legal and social consequences of incautious discharge of chronic patients from mental hospitals are discussed. Doubts concerning the efficacy of "community care" in the treatment of the chronic psychotic, in the London area at any rate, are expressed.

I gratefully acknowledge the courtesy shown and help given by the governors, medical officers, and officers of H.M. Prisons. Thanks are also due to the many mental hospitals which kindly co-operated in the investigation, and to Dr. J. H. Watkin, physician-superintendent of Horton Hospital, for permission to publish this paper.

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TREATMENT OF STAPHYLOCOCCAL INFECTIONS WITH "FUCIDIN"

BY

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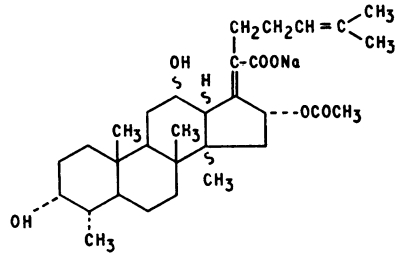
The object of this communication is to report clinical experience with "fucidin" in the oral treatment of a series of chronic and acute staphylococcal infections.

The isolation of fusidic acid, of which fucidin is the sodium salt, from the fermentation broth of *Fusidium coccineum*, a fungus which is parasitic on the plant Veronica (K. Tubaki), was reported by Godtfredsen *et al.* (1962a).

Chemically the drug is related to cephalosporin P_1 (Baird *et al.*, 1961) and helvolic acid (Allinger and Coke, 1961), and is believed (Godtfredsen and Vangedal) to have the following steroid structure:



Despite its perhydrocyclopentenophenanthrene nucleus, fusidic acid would not be expected to exhibit hormonal properties. The methyl group at C_{13} is lacking in fusidic acid and the side chain at C_{17} differs from that of steroid hormones. The oxygen function at C_{11}, which is necessary for glucocorticoid effect, is also missing.

Microbiological studies have been reported by Godtfredsen *et al.* (1962b), Barber and Waterworth (1962), and Hilson (1962) and clinical studies by Scowen and Garrod (1962) and Taylor and Bloor (1962). Fucidin is mainly active against Gram-positive micro-organisms and neisseria. Its activity against Gram-negative bacilli and fungi is extremely low. No cross-resistance exists between fucidin and other antibiotics in common use. Cross-resistance, however, is found with cephalosporin P_1.

Materials and Methods

Twenty patients were treated with fucidin. They all had serious staphylococcal infections. In some cases the infections were of long standing (nearly two and a half years in Case 1) and in others they were acute. The organisms were isolated and identified by standard techniques, including phage-typing. The sensitivity of the organism to fucidin and other antibiotics was determined before fucidin therapy was begun. The sensitivity disks for fucidin contained 10 μg. of fucidin. In all cases repeated specimens were taken for bacterial culture and any strains of staphylococci reisolated during treatment were examined for sensitivity to fucidin.

Before, during, and since treatment haemoglobin estimations, white-cell counts, and blood-film examinations were carried out in all cases. Urine was examined for albumin, casts, and red cells, and routine liver-function tests (serum bilirubin, serum alkaline phosphatase, thymol turbidity, zinc turbidity, and plasma-protein estimation) were performed.

Patients were observed clinically for possible hormonal effects, and in those who received large quantities of the drug assays of urinary 17-oxosteroids were made.

The total dosage of fucidin ranged from 150 g. over a period of 12 weeks (Case 1) to 5 g. over a period of five days (Case 10). The daily dosage ranged from 250 mg. four times daily to 500 mg. four times daily.

In most of the first 15 cases fucidin was administered alone, but in a few cases other antibiotics were used in combination to deal with a mixed infection. In the last five cases it was administered along with novobiocin.

Case 1

The patient was a man aged 33. In November, 1958, he was seen in another hospital with an extensive osteomyelitis of the right side of the pelvis and right femur, and multiple lung abscesses. Sputum culture grew a "coagulase-positive staphylococcus" sensitive to chloramphenicol, eythromycin, and tetracycline. He was treated in the first instance with chlortetracycline, chloramphenicol, and novobiocin in various combinations for five weeks, and transferred to our care with the diagnosis (incorrect) of osteogenic sarcoma of the pelvis, with multiple pulmonary metastases.

In January, 1959, the hip was explored under massive tetracycline cover and copious pus evacuated. He was subsequently nursed in a frame. Tetracycline was continued in three three-months courses during the next 12 months, tetracycline-sensitive staphylococcal pus being aspirated from the hip on several occasions, and tetracycline injected direct into the joint.

From December 8, 1959, to December 1, 1960, he was readmitted to hospital on five occasions with an exacerbation of the osteomyelitis. During this time three eight-weeks courses and one 12-weeks course of tetracycline (1 g./day by mouth) were given. On several occasions some 100 ml. of pus was aspirated from the hip-joint, but on only one occasion, after two injections of tetracycline (500 mg.) into the abscess cavity, was the pus sterile. Relapses occurred eight weeks, two weeks, three weeks, and two weeks respectively after the end of each course of tetracycline.

On December 1, 1960, a particularly severe exacerbation of his infection occurred, which was controlled by intravenous tetracycline, then intra-articular methicillin, followed by a 10-day course of intramuscular methicillin. On this occasion hip aspirations became sterile, but relapse occurred within three weeks and he was readmitted on February 11, 1961.

Between February 11, 1961, and February 27, 1962, four exacerbations occurred, necessitating admission to hospital. He had courses of tetracycline for 12 and 17 weeks, relapses occurring one month after the first course, during the second course, and 14 weeks after completion of the second course. During this year staphylococcal pus was aspirated or drained surgically on several occasions, the organism remaining sensitive to tetracycline.

He was readmitted on February 27, 1962, with high temperature, pain, redness, and swelling in front of the right hip. Chloramphenicol and tetracycline, 1 g. of each daily, was given for 14 days, but his temperature remained hectic.

On March 10 60 ml. of pus was evacuated, which grew *Staphylococcus pyogenes*. Fucidin 500 mg. six-hourly was given, nothing being injected into the hip-joint. A further 60 ml. of pus was evacuated on March 14 and on March 15 which grew *Staph. pyogenes*. On March 19 60 ml. of pus was aspirated; this showed degenerate Gram-positive cocci on Gram films but was sterile on culture. On March 23 30 ml. of pus was aspirated; it showed a few degenerate Gram-positive cocci but was sterile on culture. Thin pus flowing from needle-track on March 30 grew *Staph. pyogenes* phage 80/81 of different antibiotic sensitivity from that previously isolated—namely, resistant to penicillin, streptomycin, tetracycline, chloramphenicol, novobiocin, but sensitive to erythromycin and fucidin. On April 24 10 ml. of sterile pus was aspirated from hip. The patient was discharged on April 27 wearing a short hip spica. He took fucidin 1 g. daily, as an out-patient. He returned to work as a telephone operator on May 5. When seen on May 19 he was very well and gained weight; the wound was dry, and he was free from pain. He continued taking fucidin. On June 6 he was well and fucidin was discontinued. The total dose received was 148 g.

On September 29 he was admitted with a painful swollen right hip, which was aspirated on two occasions; mucopus, which was sterile on culture, was obtained. The inflammation settled with rest in bed. He was allowed home three weeks later, and has remained well since.

Case 2

A woman aged 47 had a spinal fusion from the second lumbar to the first sacral vertebra performed, using "bank bone," on December 4, 1959. The operation was to stabilize a painful lumbo-sacral junction. On December 10 the wound began to discharge copiously. *Staph. pyogenes* phage 52/52A/79/80/81/3A/6/7/47/53/54/42E was grown, sensitive to chloramphenicol, erythromycin, and novobiocin. Courses of chloramphenicol, erythromycin, and novobiocin were given for 10 days, 10 days, and three weeks respectively, after which the wound was explored.

The wound continued to discharge copiously, despite antibiotics, for almost a year, when the sinus was re-explored and a course of methicillin given. The methicillin had to be discontinued after 10 days because of soreness of the injection sites. The sinus dried up and remained healed for several months after the use of methicillin.

On August 1, 1961, the discharge recurred, and *Staph. pyogenes* phage type 6/7/47/54+ was cultured, sensitive to methicillin, novobiocin, and chloramphenicol. During the next 12 months the wound continued to discharge staphylococcal pus despite curettage and the administration of chloramphenicol, novobiocin, and methicillin.

On February 3, 1962, wound swab showed *Staph. pyogenes* only, phage type 52/52A/79/80/81/3A/6/7/47/53/54/42E+ resistant to penicillin, streptomycin, tetracycline, but sensitive to chloramphenicol, erythromycin, novobiocin, methicillin, and fucidin. Fucidin 250 mg. six-hourly was given. On February 10 a swab from the sinus was sterile. On February 22 a swab from the sinus grew no *Staph. pyogenes*, but a *Proteus vulgaris* sensitive to streptomycin and chloramphenicol. Streptomycin was given, 1 g. twice daily for seven days, in addition to the fucidin, which was then continued at home until March 21, when

the wound was dry, and fucidin was then stopped (total 46 g.).

On March 30 firm thumb pressure over the scar produced a bead of pus which grew *Staph. pyogenes* still sensitive to fucidin, which she was given in a dosage of 500 mg. four times daily as an out-patient. On April 9 a swab from a small amount of serum expelled by pressure on the scar showed *Pr. vulgaris* only. On the 14th a bead of serum cultured *Staph. pyogenes,* again sensitive to fucidin. On April 25 the wound was dry and fucidin was stopped (total 98 g.). On May 30 deep pressure produced a bead of pus from the healed-over sinus. Culture grew no *Staph. pyogenes* or *Pr. vulgaris.* The sinus was quite healed and dry on July 14, 12 weeks after the cessation of fucidin.

Case 3

This patient, a youth aged 18, had a Bankart operation on September 16, 1960, for recurrent dislocation of the right shoulder-joint. The wound became infected with *Staph. pyogenes,* and continued to discharge staphylococcal pus intermittently for 18 months, despite exploration and the administration of chloramphenicol, novobiocin, and methicillin (to which he became allergic).

After the course of methicillin (nine days) the wound healed for several months, but he reported again on February 10, 1962, with an increasing amount of discharge, which grew *Staph. pyogenes* phage 80/81 and which was unaffected by a three-weeks course of tetracycline. On March 7 fucidin was started alone, 250 mg. six-hourly. The discharge was almost nil on March 21, and a culture from the sinus mouth after squeezing out a "bead of serum" was sterile. The patient volunteered that "the shoulder was better than at any time since the operation," in that it felt "more comfortable." Fucidin was stopped. On March 30 a tiny bead of pus expressed on deep pressure cultured *Staph. pyogenes* sensitive to fucidin, which was started again at a dosage of 500 mg. three times daily. By April 18 the sinus was healed and fucidin was stopped (total 32 g.).

Case 4

A woman aged 78 had wound infection after McGloughlin pin-and-plate operation for intertrochanteric fracture of femur. The operation was carried out on January 5, 1962. Post-operatively, a serosanguineous discharge developed, which later became secondarily infected with *Staph. pyogenes* phage 80/81. Gross suppuration failed to respond to chloramphenicol (10 days) or methicillin (six days). The wound healed soundly with the pin and plate *in situ,* after a 25-day course of fucidin (total 25 g.).

Case 5

A man aged 55, who was treated with tetracycline for a coliform peritonitis following a perforated appendix on April 9, 1962, developed extensive bilateral staphylococcal bronchopneumonia which failed to respond to chloramphenicol. By April 19 he was moribund, and fucidin was given (500 mg. six-hourly). He had improved by April 21, and the chest *x*-ray film showed remarkable clearing. On May 5 a little coughed-up sputum was sterile, and the chest *x*-ray film was clear. Total dose of fucidin was 46 g.

Case 6

This patient, a man aged 52, who was operated on for acute appendicitis on February 16, 1962, developed a large subphrenic abscess. The pus initially grew *Escherichia coli, Streptococcus faecalis,* and *Clostridium welchii.* Penicillin and tetracycline were given. Later *Staph. pyogenes* phage 80/81 was cultured from the copious pus which was draining from the original wound. On April 22 fucidin was begun at a dosage of 500 mg. six-hourly.

On May 5 a catheter passed up to the subphrenic space from the appendicectomy wound (position confirmed radiologically) drained 60 ml. of pus which was sterile. By May 15 the wound was healed and dry, and no abscess could be demonstrated radiologically. The patient has since had an incisional hernia repaired without incident.

Case 7

A man aged 61 was treated with tetracycline after an abdomino-perineal resection of the rectum. He developed extensive consolidation of the upper lobe of his left lung, and produced copious purulent sputum containing a mixed growth of *Staph. pyogenes* phage 80/81 and *Haemophilus influenzae.* He was treated with chloramphenicol, tracheotomy, and a steam-tent.

After a three-weeks course of chloramphenicol he was much better, but still produced large amounts (30–40 ml. a day) of sputum, containing *Staph. pyogenes* phage 80/81 and *H. influenzae,* and his chest *x*-ray picture still showed extensive consolidation with cavity formation of the left upper lobe. Fucidin 500 mg. six-hourly was given. Within seven days the sputum grew only *H. influenzae,* and during the next three weeks the productive cough ceased, and the radiographic appearance of the chest approached normal. Total dose of fucidin was 47 g.

Case 8

A man aged 23 developed staphylococcal bronchopneumonia after vagotomy and gastro-enterostomy. The infection was mixed—that is, *Staph. pyogenes* phage 80/81 and *H. influenzae.* The sputum became negative for *Staph. pyogenes* after five days' treatment with fucidin. The *H. influenzae* disappeared spontaneously. Total dose given, 6 g.

Case 9

A man aged 74 developed extensive bilateral staphylococcal bronchopneumonia after total cystectomy for carcinoma of the bladder. He was given *Staph. pyogenes* phage 80/81, but died five days after starting fucidin. No staphylococci could be cultured from mucopurulent sputum obtained immediately before death.

It is of interest to record that cerebrospinal fluid obtained post mortem, approximately five hours after a 500-mg. dose of fucidin, was found to contain 5 μg. of fucidin per ml. of C.S.F. when assayed microbiologically 48 hours later. A full post-mortem examination was not carried out.

Case 10

This patient, a man aged 58, developed a staphylococcal wound infection (phage 80/81) after Jaboulay's operation. The discharge lessened but did not cease after six days' treatment with methicillin. A swab grew *Pr. vulgaris* only at this stage, and he was given a five-day course of chloramphenicol. The discharge increased, and a swab showed *Staph. pyogenes* phage 80/81, again associated with a sustained pyrexia of 100–102° F. (37.8–38.9° C.). Fucidin 500 mg. six-hourly was given, and next day his temperature dropped to normal and remained so. Within five days the wound was healed and dry. Total dose of fucidin was 5 g.

Case 11

A woman aged 23 had a large staphylococcal breast abscess (phage 80/81), which was treated for five days at home with novobiocin, prior to incision. Novobiocin was continued for 48 hours post-operatively, pending culture reports. The wound had gross cellulitis around it and she was still pyrexial 48 hours after incision, when fucidin was given, 500 mg. three times daily. The next day the cellulitis had gone, and she was apyrexial. On the third day of fucidin therapy a further loculus of pus was evacuated and found to be sterile. After eight days the breast had healed. Total dose of fucidin was 12 g.

Case 12

A man aged 52 developed bilateral staphylococcal lung abscesses after nephrostomy, which was performed to treat anuria due to a mass of malignant para-aortic glands, secondary to a carcinoma of the bladder. He died three days after cessation of a short course of fucidin (10 g.).

Post-mortem examination of the respiratory system showed mucopus in the upper tract. The right upper lobe was a mass of intercommunicating pus-filled abscesses, which grew *Staph. pyogenes,* resistant to fucidin (phage 83 AW). A smaller abscess at the base of the right lower lobe produced a *Staph. pyogenes* (phage 80/81) sensitive to fucidin.

Case 13

This patient, a woman aged 23, who had a breast abscess with severe constitutional disturbances, vomited profusely 10 to 15 minutes after taking fucidin in gelatin-coated capsules. She complained of " feeling extremely dizzy, with blurring of vision " for three to four hours after each dose. Later, when she was better, a trial dose of enteric-coated fucidin capsules caused the onset of similar symptoms after a delay of one hour.

Case 14

This patient, a man aged 56, who was treated with tetracycline after cholecystectomy, developed diarrhoea, which became alarmingly profuse and watery. Culture showed *Staph. pyogenes* phage 53/54/75/77. Fucidin was begun (500 mg. six-hourly), and within 36 hours solid motions were passed, from which staphylococci could not be cultured. Total dose was 10 g.

Case 15

A girl aged 9 was extremely ill with gross cellulitis of the right side of the face, including the orbit, cheek, right side of nose, lips, and a large swelling of the palate. After a five-day course of methicillin she became worse, with impairment of eye movements on the right side. On July 25, 1962, both upper incisor teeth were extracted, but only a little thin pus, which grew *Staph. pyogenes,* was drained. On July 27 her condition had deteriorated, and fucidin 500 mg. six-hourly was given. The septal swelling was incised, infected clot was evacuated, the right antrum was punctured, and mucopus which grew *Staph. pyogenes* was obtained.

During the next few days the child improved rapidly, the facial swelling subsided, the temperature settled, and eye movements became normal.

On August 1 a swab did not grow *Staph. pyogenes.* Fucidin was stopped (total 8 g.).

Cases 16–20

These five patients were treated with fucidin and novobiocin together (250 mg. six-hourly) as a first choice. All had tetracycline-resistant staphylococcal infections.

One patient (Case 16) had extensive soft-tissue and bone infection of the pelvis, after a fracture of the pelvis compound into the vagina, with rupture of the bladder. The staphylococci were eliminated after only five days' treatment, and pus had disappeared after a further five days.

In the other four cases the infections were post-operative, and all resolved and healed with remarkable rapidity.

Discussion

Before accepting the value of a new antibiotic it is desirable that it should be compared with currently used antibiotics for effectiveness, the emergence of resistant strains, freedom from side-effects, and ease of administration. It is therefore appropriate to test a new drug of this nature in the first instance against cases which have proved refractory to available antibiotics, and then, provided a favourable response is achieved and no serious side-effects are observed, the scope of the evaluation can be extended to include the treatment of acute infections in patients who have not had previous antibiotic therapy.

This series includes cases of acute and chronic staphylococcal infections of osseous and soft tissues, including the respiratory and intestinal tracts. The effectiveness of fucidin is considered below.

Effectiveness against Staphylococci

Staphylococcal infections have been eradicated in 17 of the 20 patients treated with fucidin.

In Case 1 (chronic osteomyelitis) pus aspirated from the hip-joint failed to grow staphylococci after nine days' treatment with fucidin. Previously, sterile pus had been aspirated only after injection of tetracycline or methicillin direct into the abscess cavity, or after many weeks of oral tetracycline therapy, and repeated evacuation of pus. Although the staphylococci could not be cultured in pus obtained from the hip-joint only nine days after commencing fucidin, the drug was continued for a long course in the hope of achieving a permanent cure of this extensive osteomyelitis. An abscess which presented three months after discontinuing fucidin therapy was sterile. Only many months' observation, of course, will show whether further relapse will occur.

In Case 6 pus from the subphrenic abscess failed to grow staphylococci after 13 days' treatment, and in Case 11 pus from a breast abscess failed to grow staphylococci after three days' treatment.

Case 7 (post-operative staphylococcal pneumonia), although very much better after tracheotomy, steam, and chloramphenicol, continued to cough up considerable amounts of sputum containing *Staph. pyogenes* phage 80/81. Within seven days of commencing fucidin, although he was still producing sputum, no staphylococci could be grown from it, and he ceased to be a danger to his fellows.

In Cases 2 and 3 post-operative staphylococcal wound infections of very long standing have been eliminated. In Case 2 there was still a small sinus which failed to grow staphylococci five weeks after stopping fucidin but which grew *Pr. vulgaris.* This healed and became dry. In this case the elimination of the staphylococcus was followed by the spontaneous disappearance of the *Pr. vulgaris,* but the reverse did not apply. This patient's sinus had healed before on treatment with methicillin. In Case 3 a chronic sinus of 18 months' duration, in a patient who developed hypersensitivity to methicillin, healed, and has remained so for 26 weeks after cessation of fucidin therapy. Also of interest in this case was the rapid disappearance of exuberant granulation tissue.

In Case 4 a staphylococcal wound infection healed rapidly despite the presence of a metallic foreign body—that is, a pin and plate. The wound has remained soundly healed for 15 weeks after cessation of fucidin therapy.

In Case 5 (confluent bilateral staphylococcal bronchopneumonia) the drug was probably life-saving. Although there was an overlap in treatment with chloramphenicol and fucidin, the sputum still grew *Staph. pyogenes* 48 hours after the chloramphenicol was stopped. The radiological clearing of the chest only 48 hours after starting the fucidin was remarkable.

Effectiveness in Presence of Pus

Godtfredsen *et al.* (1962) have demonstrated that the *in-vitro* activity of fucidin is considerably decreased in the presence of serum. Clinical experience in this trial (Cases 1, 6, 11, and 16) suggests that fucidin exerts a potent antibacterial effect even in the presence of large collections of pus, into which it apparently penetrates in effective concentrations.

On a number of occasions specimens of pus in the above patients failed to grow staphylococci under *in-vitro* conditions, and were reported as being "sterile." Evidence, however, is lacking whether the sterilization was apparent (a bacteriostatic phenomenon due to carry-over of fucidin) or real (a total bactericidal effect). This point is worthy of further investigation, as it has been recorded by Taylor and Bloor (1962).

Effectiveness in Pulmonary Infections

Mitchell *et al.* (1961) have drawn attention to the facility with which patients with chronic lung disease develop staphylococcal lung sepsis if they are in hospital for more than seven days. They further point out that lung infection is commonly an accessory and occasionally a primary factor in death after abdominal operations. In all five staphylococcal pulmonary infections in this series (Cases 5, 7, 8, 9, and 12) the organism was acquired in hospital after abdominal surgery. In two patients (Cases 9 and 12), both of whom had widespread malignant disease, it was a contributory cause in their deaths. Fucidin controlled the pulmonary infection in four of these cases, and was considered to be life-saving in one (Case 5).

A patient who died of widespread malignant disease (Case 12) was found at necropsy to harbour a fucidin-insensitive staphylococcus, following inadequate chemotherapy (see below).

In accord with the expressed opinion of Mitchell *et al.* (1961), that a major reservoir of hospital staphylococci is the lungs of infected patients, Case 7 was given fucidin for the main purpose of removing a source of staphylococci phage 80/81. This patient had made a satisfactory clinical response to chloramphenicol, and his life was no longer in danger because of his staphylococcal lung infection, but he continued to expectorate staphylococcal sputum prolifically. Seven days after starting a course of fucidin his sputum failed to grow staphylococci, and he was able to leave isolation and be transferred to a convalescent home, where he continued fucidin therapy.

The prompt administration of fucidin in Case 8 quickly controlled the temperature and eliminated the staphylococci from the sputum.

Effectiveness in Staphylococcal Diarrhoea

Staphylococcal diarrhoea, associated with tetracycline therapy post-operatively, was rapidly controlled in Case 14. It is to be expected that fucidin would be effective in staphylococcal gastro-intestinal infections, as it appears to be mainly excreted in the bile, and is found unchanged in the faeces. Furthermore, it has no effect on Gram-negative bacteria, and would not be expected to disturb the normal gastro-intestinal flora.

Effectiveness in Presence of Mixed Infections

Arndt and Ritts (1961) reported that a synergism exists between *Staph. aureus* and *Pr. vulgaris*. Their work suggests that the primary objective in a mixed infection should be the eradication of the staphylococcal element, which is responsible for the enhancement of the virulence of the proteus.

Mixed proteus and staphylococcal infections were seen in four cases (Nos. 2, 6, 9, and 10). In these (except Case 9, the patient who died of malignant disease during treatment) elimination of the *Staph. pyogenes* was followed by the spontaneous disappearance of the *Pr. vulgaris*, but the reverse did not apply.

A mixed staphylococcal and *H. influenzae* lung infection behaved similarly (Case 7). Penicillin and chloramphenicol successively failed to eliminate the *H. influenzae*, but when the staphylococcus was eradicated with fucidin the *H. influenzae* gradually disappeared without a specific antibiotic being prescribed for it.

It occurs to me that stopping the antistaphylococcal therapy too soon in the presence of a discharging wound associated with a secondary organism might well allow relapse, owing to reinfection with staphylococci. Persistence with antistaphylococcal drugs until healing occurs allows spontaneous disappearance of the secondary organism.

The success in treating staphylococcal wound infections by isolating the patient and by strict barrier nursing is no doubt due to prevention of reinfection. This ideal is unfortunately difficult to achieve in most busy surgical units, and antistaphylococcal treatment needs to be continued until the wound is healed.

In Case 2 there was a changing strain of staphylococci, no doubt due to repeated reinfection, and similar reinfection appears likely but not proved in Case 3.

In Case 10, despite the disappearance of *Staph. pyogenes* after six days' methicillin, a continuing wound discharge associated with *Pr. vulgaris* became reinfected with staphylococci. Rapid healing occurred when fucidin was started.

Effectiveness in Combination with Novobiocin

Novobiocin and fucidin are synergistic antistaphylococcal antibiotics. In Cases 16–20 infection was quickly eradicated, although in this short preliminary series it was not possible to know whether elimination of staphylococci was quicker than it would have been with either drug alone.

There is evidence, however, that this combination may reduce the emergence of resistant strains of staphylococci.

Emergence of Resistant Strains of Staphylococci

From one patient in this series a staphylococcus resistant to fucidin was grown. This patient (Case 12) had a mixed staphylococcal lung infection. He died from widespread malignant disease, and at necropsy pus taken from the lower lobe of the right lung grew *Staph. pyogenes* phage 80/81, sensitive to fucidin, and pus taken from an abscess in the upper lobe of the right lung grew *Staph. pyogenes* phage 83 AW, resistant to fucidin. The patient had had five days' fucidin therapy (2 g./day), treatment being stopped three days before death. Before starting treatment with fucidin in this patient *Staph. pyogenes* phage 80/81 sensitive to fucidin was cultured from his sputum, and on the fourth day of treatment sputum failed to grow staphylococci.

One other patient, treated in this hospital but not included in this series, had a mixed staphylococcal

infection, associated with multiple lung abscesses. Two of his three strains of staphylococci were sensitive to fucidin, and one was resistant. It is not certain whether the resistant strain emerged during treatment or whether it was present before treatment commenced. The presence of fucidin-resistant staphylococcal infections emphasizes the need for strict bacteriological control of fucidin therapy.

In Case 2 a *Staph. pyogenes* reisolated after nine weeks' treatment with fucidin was still sensitive to the drug, and the infection of three and a half years' standing was eliminated after further treatment with fucidin.

Barber and Waterworth (1962), Godtfredsen *et al.* (1962a, 1962b), Hilson (1962), and Taylor and Bloor (1962) have reported the ready development of fucidin-resistant variants *in vitro*. Barber and Waterworth comment that any large inoculum of staphylococci contains a few mutant organisms which show a considerable degree of resistance to fucidin.

While acknowledging the validity of *in-vitro* observations, one cannot ignore the observation of Taylor and Bloor (1962), which has been confirmed in this study, that the facile development of fucidin-resistant staphylococci *in vitro* is not reflected in the proper clinical use of the drug.

In situations in which subinhibitory concentrations of the drug are administered to large inocula of organisms, selective overgrowth of more resistant strains is encouraged. Such a situation is apt to occur when fucidin therapy is withdrawn prematurely, the falling tissue concentrations presenting a diminishing challenge to surviving organisms and thereby enhancing the resistance index of a given inoculum.

Thus patients with infected burns, or large accumulations of avascular, necrotic, or coagulated material in which staphylococci are harboured, must be regarded as particularly prone to develop fucidin-resistant organisms.

Although in this series the use of fucidin alone has in most cases been effective in eliminating staphylococcal infections, it might well be wise to consider the use of fucidin in combination with other antibiotics in circumstances where the emergence of resistant organisms would appear to be particularly apt to occur.

Synergism has been demonstrated *in vitro* between fucidin and penicillins V and G even when the organism is resistant to penicillin (Godtfredsen *et al.*, 1962a, 1962b; Barber and Waterworth, 1962; Scowen and Garrod, 1962). Similar synergism exists between fucidin and erythromycin.

The emergence of resistant organisms is reported to be significantly retarded when fucidin is used in combination with novobiocin (Tybring, 1962).

Toxicity

No toxic effects have been revealed by blood counts, liver-function tests, or examination of the urine, despite prolonged and large doses of fucidin in some cases.

A number of patients complained of epigastric burning pain during the first few days of treatment. This usually passed off spontaneously after four or five days even when the drug was continued, and in most cases the discomfort was easily controlled by aluminium hydroxide suspension.

One patient (Case 13) was unable to tolerate fucidin. She vomited profusely after each dose, and complained of dizziness, blurring of vision, and itching of the skin. When skin-tested no allergy to fucidin was detected, but some days later there was a similar though much milder reaction to enteric-coated capsules, though these were not available at the time of commencing treatment, and the fucidin had to be withdrawn. This patient gave no previous history of drug allergies or of undue liability to vomit. She was, however, extremely toxic, with a temperature of 104° F. (40° C.), and this may well have increased the sensitivity of her vomiting centre.

Absence of Hormone Effects

Despite the fact that the structural formula of fucidin does not suggest that it will have hormonal properties, it was thought it would be of interest to watch carefully for any adrenocortical effect, especially in patients who had had large doses of fucidin.

No patient showed any clinical signs of adrenocortical disturbance.

In the two patients (Cases 1 and 2) who received large doses of fucidin (148 and 98 g. respectively) no significant alteration was found in the 24-hour excretion of 17-oxosteroids (native or total) before, on three occasions during, and again at the end of the course of fucidin.

The two patients (Cases 9 and 12) who died of malignant disease showed no macroscopic or microscopical abnormalities in the suprarenal glands. They, however, had had only a small quantity of fucidin (5 g. each).

Ease of Administration.—Fucidin has been effective orally in eradicating sensitive staphylococcal infections. In one case the drug had to be withdrawn because of persistent vomiting.

Conclusions and Summary

Fucidin administered orally in a dosage of 250 to 500 mg. six-hourly has been confirmed to be an effective antistaphylococcal antibiotic. Twenty patients with staphylococcal infections of bones, joints, soft tissue, lungs, and gastro-intestinal tract were treated and in 17 the staphylococci were eliminated. Two patients died of widespread malignant disease before treatment could be completed, and one patient was unable to tolerate the drug.

Unless strict isolation and barrier nursing can prevent reinfection with staphylococci, it is suggested that fucidin treatment of staphylococcal wound infections should be continued despite negative culture reports, and especially if *P. vulgaris* is also present, until healing has occurred.

The emergence of resistant strains in this series has not been a problem. It does occur, however, with great facility *in vitro* (Taylor and Bloor, 1962). The exposure of staphylococci to the drug in inadequate concentrations will facilitate the overgrowth of less sensitive mutants in patients as in the laboratory. This occurred in one patient in this series. Such resistant mutants have been demonstrated to occur in large inocula (Barber). A policy of combined therapy with fucidin and a suitable non-antagonistic antibotic might prove to be the most desirable way to delay the emergence of resistant staphyloccocci. The emergence of resistant organisms has been reported to be retarded by the use of fucidin in combination with novobiocin. In a preliminary short series of five patients this combination was effective.

No serious toxic effects were observed in this series. No changes occurred in liver-function tests, blood

pictures, or renal functions, despite one patient receiving as much as 150 g. of fucidin over three months. No hormonal effects could be detected. Many patients complained of nausea and epigastric pain during the first few days of treatment. This was reduced to a minimum by administering fucidin just before meals or after a dose of aluminium hydroxide suspension. One patient vomited profusely after fucidin, and complained of dizziness, blurring of vision, and itching of the skin. Fucidin had to be stopped and her symptoms quickly disappeared. Another patient who vomited when given fucidin in gelatin capsules was able to tolerate the drug in enteric-coated capsules.

Of particular interest has been the effectiveness of fucidin in the presence of large collections of pus, despite the fact that it is known to be bound to a considerable degree to plasma proteins.

I would like to thank the many consultants under whose supervision these patients have been treated, and the nursing staff who have cared for them so well. Advice and technical assistance have been willingly forthcoming from the medical and technical staff of Broadgreen Hospital Laboratory. I have drawn quite freely on Dr. A. Darragh's extensive knowledge of the pharmacology of antibiotics. Leo Laboratories have provided generous supplies of fucidin, often at short notice, through the efficient liaison of Mr. J. Kelly.

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A TRIAL OF XENALAMINE

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Recently published reports suggested that a new synthetic antiviral agent xenalamine (*p*-[α-ethoxy-*p*-phenylphenoxyamido]benzoic acid) might be of value in the treatment of measles infections. De Mattia and Rapellini (1961) treated 32 children and 28 adults and reported that in the adult cases xenalamine exerted a beneficial effect. Magni (1961) reported that the drug was of benefit in 10 out of 13 patients treated. On the other hand, Nordio and Massimo (1961) treated 20 patients with xenalamine and found no evidence that the drug had any effect on the illness. Baldini and Vaccari (1961) also failed to find any evidence of chemotherapeutic action in their small series of five treated cases. Rasi (1961) treated 94 patients, and suggested that xenalamine might be of value in reducing the severity of the disease if given early enough. The dosage employed by all workers was 50–100 mg./kg./day. No toxic effects of the drug have been reported.

Measles is a severe disease in Nigerian children, affecting mainly those under 3 years of age, and causing an estimated 4% case mortality (Gans *et al.*, 1961). The main cause of death is bronchopneumonia. Clearly a drug which would reduce the severity of the disease and the incidence of bronchopneumonic complications would be of great value.

In view of the conflicting reports in the literature, it was decided to undertake a controlled trial to establish whether xenalamine, given in a dose of approximately 50 mg./kg./day, would prove of value in the treatment of measles under local conditions.

Methods

A preliminary clinical study was made on 30 consecutive Nigerian children attending the out-patient department of the University College Hospital, Ibadan, who were suffering from early measles. The children were examined daily, and unless complications supervened were given only a linctus and chloroquine, the latter because of the possibility that malaria was also present. Of the 30 children, 28 were over 6 months and under 3 years of age, one was 3 years, and one 4 years old.

By this means an accurate picture was obtained on the natural history of the disease in Ibadan, thus assisting the statistical design of the present trial. A detailed description of the natural hisory of measles in Nigerian children will be the subject of a further communication by one of us (K. C.).

In view of the age incidence found in the preliminary study, the trial was limited to children in the age-group 6 months to 3 years. As it is unusual for measles to be diagnosed in the prodromal stages in Nigeria, cases selected for the trial were restricted to those in whom the rash had appeared within 24 hours of first attendance at the out-patient department. Any children showing complications at this stage were excluded.

It was decided to use a sequential design of restricted type (Armitage, 1961) for the trial. Analysis of the preliminary series of 30 consecutive untreated cases of measles showed that respiratory complications occurred in 11, conjunctival injection in 20, and diarrhoea in 19. Bacteriological examination of the stools from those children with diarrhoea revealed a recognized pathogen (Shigella) in only one case. It was decided to design the

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