exposure to the fumes of nitric acid, nitrous dioxide, hydrogen sulphide, and as was seen following the Coconut Grove fire in Boston, inhalation of fumes.

In all these cases absolute rest with morphine and the administration of oxygen with humidification under pressure if possible is indicated. If shock is present intravenous plasma or serum may be given, but not more than 2,000 c.c. Oedema may occur during the administration of anaesthetics such as ether and N_2O . When this happens the table may be tilted to help drainage from the lungs, and pharyngeal or intratracheal intubation carried out with pure oxygen given under pressure. Atropine gr. 1/100 must also be given intravenously. In cases due to cerebral oedema intravenous hypertonic solutions such as 50 per cent. succhrose are of benefit together with pharyngeal and intratracheal intubation with suction when necessary. The oedema following rapid paracentesis is now uncommon, presumably due to improved technique.

In past pandemics of influenza rapidly occurring oedema was often seen, but with the present attacks it is uncommon. It should be treated when it occurs with humidified pure oxygen.

In conclusion it is hoped that the foregoing summary will have shown the variety of conditions in which pulmonary oedema may arise. The exact vagal and sympathetic distribution to the lungs is not yet quite clear, and the importance of the interplay of vascular and central nervous reflexes remains yet to be elucidated. It is possible that the stretching caused by capillary engorgement, initiates reflexes giving rise to increase of permeability.

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PENICILLIN IN GENERAL PRACTICE

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Introductory

This lecture purports to be no more than an elementary summary of what is generally known about penicillin at the present moment, and it is as well to state at the outset that a good deal of that knowledge is still of a tentative nature. In treatment particularly, the establishment of a remedy and its method of use depends not upon the reported cure of a few, but of a statistically significant number of

cases—a criterion which has not yet been fulfilled in the case of many diseases now coming under penicillin treatment.

You will find, therefore, that you are in some sense thrust into the position of experimenting upon your patients, that cut and dried procedures are not yet wholly the guide but are going to be partly the result of your efforts. Ordinary streptococcal tonsillitis may serve as an instance; does it always, as some say, or

does it sometimes, as others say or does it never yield to penicillin lozenges? With Vincent's organisms, the kill by the lozenge is definite, but with the more invasive streptococcus perhaps it is necessary to give injections of penicillin as well and, if so, perhaps the more comfortable sulphonamide tablet may prove no less efficient. That is one thing which you in your practices will find out.

Now let us proceed to follow the synopsis which is provided because the subject involves a good deal of detail and of figures not easily carried in the head.

History

1. *Early Work.* The green mould penicillium notatum was described by Westling in 1911. It consists of the usual mass of microscopic threads, some with fingers (the penicillus) from which spores are shed. Most creatures tend to regard their neighbour with rather a jealous eye; if you are a viper you may make a venom which will clot his blood; if you are a man you may put a lock on the front door or turn yourself into a limited liability company; if you are a mould you may make an antibiotic. There are many examples of such antibiotics: gramicidin, the product of a bacillus, streptomycin, that of a soil fungus, helvolic acid, that of a mould, active against tubercle bacillus yet, unfortunately, poisonous to the liver. The antibiotic principle of penicillium notatum was observed by Fleming in 1928, who named it penicillin, who found it active against a wide variety of bacteria *in vitro* and who produced crude unstable solutions of it.

2. *Second Attack.* It was the arrival of the sulphonamides in the 1930s that exploded the popular medical myth of the therapeutic invincibility of bacteria ensconced in the tissues and revived the old notion of *therapia sterilans magna*. This led to a second investigation of penicillin by a group of workers under Florey in Oxford, who succeeded in producing a stable, dry, concentrated penicillin, publishing their results in 1940.

3. *Present Stage.* Owing to war conditions here, mass production was started by the Americans, who used a new strain of peni-

cillium (chrysogenum instead of notatum) more suited to deep culture, which they substituted for the earlier surface method, developing the thoroughly practical engineering process now adopted also in England.

Method of Manufacture

Large hermetically sealed tanks are charged with cornsteep medium and sterilized by blowing steam through them. After inoculation the process of deep fermentation is maintained by bubbling sterile air through the culture and by controlling the temperature. When the yield is maximal the fluid is filtered from the mould, concentrated by organic solvents and absorption procedures till it contains about 10 per cent. solids, and dried frozen with the penicillin in the form of calcium or sodium salt.

2. *Action.* Penicillin destroys certain bacteria in their growing phase. Sometimes they can be seen to swell up before disintegrating under its influence. The chemical nature of this action is at present unknown. In the synopsis (see Appendix A) is given a list of micro-organisms arranged in penicillin-sensitive and penicillin-resistant groups. But, like human courage, penicillin-resistance is not an absolute quality possessed by one and not another. Some have more, some less, and the display may vary with circumstance. Courage in battle has been ascribed particularly to the male, but you must all have noticed how the roles have been reversed in the donors' panels. There are reports that meningitis due to Pfeiffer's bacillus (*haemophilus influenzae*) has been cured by intrathecal injections of large doses of penicillin. Thus it seems that, faced with a penicillin lozenge, Pfeiffer's bacillus may survive, yet boxed up with penicillin in the meninges (from which the leak is slow) it may perish. Another situation where penicillin acts at an advantage is the urinary tract, into which it can be poured (so facile is its excretion) like Niagara Falls, and where it has been said to be capable of sweeping away even the highly resistant proteus.

However, it is not wise to concentrate on exceptions. The golden rule is that before treatment with penicillin you should establish the sensitivity of the organism you are attacking. Roughly speaking, an organism may be said to be sensitive if it is not more than ten times as resistant as the standard Oxford staphylococcus.

3. *Path of Penicillin in the Body.* Penicillin is very rapidly absorbed after injection, penetrates everywhere except to the tears and cerebro-spinal fluid, and is quickly excreted. Saliva and the interior of the red blood cells are less penetrable than other tissues; normal or acutely inflamed serous sacs are penetrated, but chronic collections of pus with fibrous walls are largely isolated from the action of penicillin. The placenta is readily permeable.

Sixty per cent of injected penicillin is excreted by the tubules of the kidney. Hence there occurs a delay in excretion if the tubules are overworked, as in nephritis, or the administration of some other tubularly excreted substance (such as amino-hippuric acid) simul-

taneously with the penicillin. Ten per cent. of injected penicillin is excreted in the bile, but in treating biliary infections it must be remembered that disease in this quarter may be caused by insensitive coliform bacteria. The remaining 30 per cent. of injected penicillin is destroyed in the body by some unknown process.

4. *Toxic Effects.* Penicillin is completely non-toxic, locally and systemically. This means that if the dosage is pushed up to some fantastic figure, and the preparation is pure, the symptoms produced will be those of poisoning by the metal (usually calcium or sodium) with which the penicillin is combined to form a salt.

Thus the only reaction to be expected from penicillin itself will be one of allergy. About 5 per cent. of our population are said to give positive intradermal tests to penicillin at the present moment. True allergic reactions have been reported (usually in the form of rashes) and are sometimes ascribed to previous sensitization by moulds. Probably most allergic reactions are due, like the other types of reaction observed, to impurities. As preparations get purer, reactions get fewer.

If a penicillin reaction threatens to curtail treatment, it is worth while testing the effect of the vehicle alone and of the penicillin alone and then, if the latter is positive, of a different make of penicillin before abandoning treatment. Reactions are commonly so trivial that treatment does not have to be interrupted. It is probably in general practice that most judgment will be required in these matters, for it is easier to ignore a reaction in a severe hospital case, such as a child with staphylococcal osteomyelitis and pericarditis, which is, moreover, under constant surveillance.

Other unpleasant effects due to impurities in the preparation are :—

(a) Thrombosis of veins in intravenous treatment.

(b) Local pain on injection.

(c) Penicillin fever (slight degrees of which are by no means uncommon and have to be distinguished from the pyrexia of the disease under treatment).

(d) Meningeal irritation in intrathecal medication (which may progress to actual damage).

(e) A slight, and still doubtful, ecchymotic action.

In other words, there is still a variable amount of irritant impurity in penicillin preparations which may be expected to lessen as time goes on. In England and the U.S.A. official tests of all batches are performed on mice so that gross degrees of toxicity are excluded.

There is also one local effect which you will meet quite commonly: this is the sore mouth which follows treatment by penicillin lozenges. Discomfort may be considerable for about a week, though there is no danger. The cause is said to be the extinction of the normal flora by the action of penicillin itself.

Finally, one should bear in mind that it is possible to get a Herxheimer reaction from penicillin, just as in the case of other anti-syphilitics, and that hepatitis may be caused (and has already been reported) by the transmission of infected blood from one patient to another. The prevention of the latter consists in sterilizing the syringe as well as the needle between patients.

5. *Effect of Animal Tissue on Penicillin Action.* Blood, pus, lymph and bacterial bodies do not decrease the power of penicillin. This is not even true of sulphonamides where, for instance, bacteriological assay is hindered by the anti-sulphonamide action of the peptone employed in the culture medium.

6. *Destruction of Penicillin.* The purer the penicillin, the more stable it becomes. It is especially sensitive to heat, water, acids, alkalis, oxidizing agents and heavy metals. Bearing these facts in mind enables one to predict its behaviour under various circumstances; instability in acids, for instance, would indicate its destruction in the stomach, and it follows also that aqueous solutions would be less stable than oily suspensions where water is excluded. Since the sodium salt is hygroscopic, the calcium salt should be the more stable. In fact, an oily suspension of the calcium salt will last for six months at cool room temperature, whereas aqueous solutions lose much potency in one week, even in the refrigerator. A point worth remembering in connection with penicillin drips is that certain kinds of tubing made from impure rubber may inactivate the solution.

Another special point is the liability of penicillin to be destroyed by the enzyme 'penicillinase,' which is made by certain bacteria, notably of the coliform group. The enzyme is not, by the way, the cause of penicillin resistance, since some bacteria which can make it are sensitive to penicillin. There are three practical conclusions to be drawn about penicillinase. One is that it is no good giving penicillin by the rectum where coliform bacteria abound. Another is that the persistence of a penicillin-sensitive microbe under treatment may be due to an accompanying penicillinase producer. The third is that if your penicillin preparation should happen to be contaminated by a penicillinase producer it will become inactive.

7. *Acquired Resistance to Penicillin.* In the laboratory and in the animal body a germ may become trained to resist the action of penicillin. There is no difference between this kind of training and any other kind. It is a question of becoming habituated by starting with small doses and working up, just as Thomas de Quincey did with his opium, or a professional juggler does with his plates. When de Quincey stopped his opium his acquired tolerance decreased. The juggler who does not practice drops a plate on his nose. In the same way acquired penicillin resistance is only temporary, often quite short, so that effective therapy can be started again after a rest. But the solution of the problem in practice lies in giving big enough doses from the start; so that tolerance is never established.

This phenomenon must be distinguished from the inborn power to resist penicillin which is very occasionally found in individual strains of penicillin-sensitive organisms.

Methods of Assay

Three main assays are required: tests of strength of preparations, of concentration of drug in body fluids and of resistance of a pathogenic microbe compared to that of standard organisms. All methods depend on comparing degree of inhibition of bacterial growth on solid or in liquid media with that of standard bacteria and standard penicillin solutions. Rough quantitative results suitable for controlling treatment are thus obtained. And sooner or later, after many cases where the

laboratory merely tells you what you already know, you will come to a case where success or failure depends upon these assays.

Therapeutics

The synopsis gives a list of official and unofficial preparations of penicillin (see Appendix B) with their times of endurance. Generally speaking, penicillin should not be mixed with other drugs, but it is useful to remember certain permissible combinations; sulphonamides are compatible when solid, but not in solution; novocain and cocain are compatible, but adrenalin in its usual acid solution is not, therefore any novocain used must be free from it; NAB is compatible; alcohol is compatible only up to 25 per cent., above this strength it rapidly destroys penicillin; chloro-cresol and phenoxetol are two antiseptics which are not destructive of penicillin in concentrations up to about 5 per cent.

Treatment

1. *General.* Penicillin represents as great an advance in treatment as did anaesthetics in the control of pain or the great bacteriological decade of 1880-90 in the diagnosis of disease. You now have in your bag a magic strong enough to deal with severe illness, and your patients know it. Hospitals are overcrowded. Patients do not like hospitals. One would expect, therefore, a tendency to reversal of the flow of cases which the practitioner sends to hospital. Whether the practitioner resists the tendency or not, whether the tendency is good or bad, it must be there. In some years' time when, say, the fluctuations in mastoid operations have been statistically analysed, it may be shown that the tendency has or has not become a fact.

This new penicillin work carries into general practice some of the responsibilities, the rewards and the requirements of hospital practice. The particular requirement which at once crops up is the laboratory. If you are to use penicillin in a scientific manner, which is the only way to use it, you need a laboratory upon your visiting list. To ignore laboratory help is like tying a bandage over your own eyes, and if you can draw the large number of syringes you are going to use, guaranteed clean, sharp and sterile from the laboratory sterilizing

department, so much the better.

2. *Route and Dose.* The object of systemic penicillin treatment is to produce and maintain for as long as necessary, a bactericidal concentration in the blood stream. This concentration, which can be measured in the laboratory, amounts to from one-tenth to one-quarter of a unit per cc. of blood. It may be produced by the following subcutaneous or intramuscular dosage:—

Aqueous, three-hourly ..	20/ 60,000 units
Oily, twice daily ..	120/200,000 "
Oily, once daily ..	300/500,000 "

There is definite evidence that the higher dosage shortens the illness; it is less likely to lead to penicillin resistance on the part of the microbe; it can harm nothing but the microbe and purse. Therefore, if there are to be two schools in penicillin therapy, common sense would recommend the high dose and not the low dose school.

Attempts to prolong the penicillin action by increasing the intramuscular dose of aqueous solution are unavailing, in spite of statements that extra dosage at night will last till morning. Here are some figures which show that the problem is like that of the Atlantic liner where, for every extra knot of speed above a certain level the amount of extra fuel required becomes increasingly greater; 10,000 units maintain the blood bacteriostatic two hours, 25,000, three hours and 100,000, four hours.

It has been said that penicillin therapy is like trying to fill a bath with the plug out. To counteract this rapidity of excretion the intermittent three-hourly intramuscular method is sometimes replaced by a drip. Intravenous drips, abandoned because of thrombosis of veins by impurities in the penicillin, may come in again now that preparations are purer. For the same reason subcutaneous injections, whose pain was caused by impurities, may again compete with the intramuscular route, for their absorption is slightly slower. The most popular form of drip hitherto used depends upon a periodical twitch being given to the plunger of a syringe connected by a rubber pipe to an intramuscular needle; this may be done manually or by some form of clock. The site of the needle has to be changed every two days or so. Patients usually prefer an intermittent method in

which the site of injection is varied by some such routine as left deltoid, triceps, buttock, thigh, right deltoid, triceps, buttock, thigh. Pain may be avoided by drawing 1 cc. of novocain solution into the syringe after the penicillin, so that it is injected first.

Local injections may be required into abscesses or serous sacs. Except perhaps in cases of achlorhydria it is useless to give penicillin by the mouth. A certain amount of sporadic absorption has, however been observed by this route, and there are still possibilities of the method being developed in time.

Transpulmonary administration of penicillin aerosol by means of some form of inhaler, such as the Collinson, or even a hand atomizer, is an effective method of giving penicillin, and probably has a future. A few cubic centimetres of solution at 80,000 units per cc. are suitable for one session.

Intermittent intramuscular injection of an oily suspension is at the present time the method of choice in general practice. A dose of 3 to 500,000 units once a day suffices to keep the blood bacteriostatic. For the average adult of 150 lbs. weight this means a dosage of 2,500 units per lb., from which figure the dose for children may be calculated.

3. *Treatment of Particular Diseases*

(i) *Spirochaetoses*. This group of dissimilar diseases includes Vincent's angina, syphilis, yaws, rat-bite fever, Weil's disease and relapsing fever. All are brought under one head through being caused by various spirochetes which are all sensitive to penicillin. Vincent's angina yields extremely well to lozenges only. The treatment of syphilis is a speciality in itself. The duration of treatment for the other members of the group is from seven to ten days.

(ii) *Meningitis*. Penicillin is stopped by the choroid plexus and must, therefore, be given intrathecally to meningeal cases. Purely cerebral disease can be reached by the blood stream. In special circumstances, cisternal or even ventricular puncture may prove necessary. In cases treated by lumbar puncture, 10 cc. of fluid are withdrawn and replaced by an equal volume of penicillin in saline at a strength of 1,000 units per cc. The pro-

cedure is repeated daily for a week. Fulminating pneumococcal cases require ten times this dosage, and it is said that cases due to Pfeiffer's bacillus may be cured by similar high dosage.

(iii) *Chests*. In the case of pneumonia the question resolves itself into one of sulphenamides versus penicillin. A reasonable solution is to give sulphadiazine or sulphamezathine for two to three days, holding penicillin in reserve. A dose of 120,000 units in 10 cc. after aspiration (and sending the pus to the laboratory) is suitable for an early empyema, giving effective concentrations in blood and pleural cavity for 24 hours. If, however, the pleura is fibrosed the penicillin will remain longer in the cavity, not being absorbed into the blood stream, but surgery may be needed in addition. In secondarily infected tubercular empyema it may be possible by means of local penicillin to avoid operation with its resulting tubercular sinus. In bronchitis, bronchiectasis and lung abscess, aerosol penicillin is indicated.

(iv) *Throats*. It may or may not be necessary (probably it is) to augment penicillin lozenges by intramuscular injection in cases of streptococcal tonsillitis which are deemed worthy of specific treatment. In diphtheria, antitoxin must also be given. For diphtheria carriers, penicillin is the treatment of choice.

(v) *Skins*. Skin disease, among the most frequent in general practice, is on the whole that in which penicillin, in whatever form, has given the most variable and disappointing results. Local treatment is successful in impetigo and in other open septic conditions maintained by penicillin-sensitive microbes.

(vi) *Burns*. Lanette wax penicillin cream is an excellent dressing in the early stage of a burn. Penicillin-resistant invaders may be discouraged by using cream incorporating 2 per cent. of phenoxetol. But it is generally better to avoid these tough secondary invaders by stopping the penicillin treatment once granulations are present, and then treating the burn on orthodox lines until the time of skin grafting (if this proves necessary), which should be preceded by a second short course of local penicillin. This avoids delay in separation of the slough, which has been observed with continuous penicillin treatment. Very

deep burns will require treatment as for wounds by systemic as well as local penicillin.

(vii) *Hand Infections*. Paronychia should be treated by penicillin cream, with or without operation. Deeper infections involving cellulitis, tenosynovitis or spreading lymphangitis will require systemic penicillin treatment as well.

(viii) *Prophylaxis*. A prophylactic course of systemic penicillin is now given as an 'umbrella' for such operations as the extraction of infected teeth, the opening of joints, grafting procedures, and tonsillectomies. In mouth operations, lozenges may also be used and have already been shown to cut short the painful period following the removal of impacted wisdom teeth.

Major wounds should receive systemic penicillin, fractures involving the central nervous system may require intrathecal penicillin, and haemothorax is treated by intrapleural penicillin.

Ophthalmia neonatorum is preventable by routine penicillin eye drops. Breast abscesses may be avoided by the routine use of penicillin cream for cracked nipples.

Cross infection in closed spaces may be greatly reduced in the future by the use of penicillin aerosols.

4. *Duration of Treatment*. Available information shows that different diseases vary fairly widely in the time taken by penicillin to control them, and also that the same disease may vary in this respect as between patient and patient. The following table (Hudson) gives some indication of these differences in response to a treatment of 60,000 units given in aqueous solution three-hourly:—

	days
Uncomplicated gonorrhoea	1
Vincent's angina	2
Erysipelas, impetigo	3
Carbuncles, cellulitis and adeno-cellulitis	5
Breast abscesses	7
Otitis media and mastoiditis	8-10
Sinusitis, pulmonary lesions and meningitis	10-12
Complicated septicaemias	12-21
Endocarditis	21-28

APPENDIX A (from Fleming)

<i>Sensitive</i>	<i>Insensitive</i>
Staphylococcus	Enterococcus
Haemolytic streptococcus	Typhoid, coli, dysentery
Streptococcus Viridans	group

Anaerobic streptococcus (some)	Proteus
Pneumococcus	Pseudomonas (B. Pyocyaneus)
Gonococcus	Haemophilus (Influenzae and pertussis)
Meningococcus	V. Cholerae
N. Catarrhalis	Tubercle (and other acid-fast bacilli)
Micrococcus	Pasteurella group (plague, etc.)
Sarcina	Brucella
Actinomyces	Friedlander's bacillus
Anthrax group	Non-pathogenic gram-negative cocci
Diphtheria group	Most of the viruses
Spirochaetes	Yeasts
Clostridia (anaerobes, tetanus, gas-gangrene, Botulinus)	Monilia (thrush)
Rickettsia and larger viruses (partly)	Moulds

APPENDIX B

Official Preparations (B.P.)

Injectio	20,000 units per cc. in saline.
Penicillini	Keeps seven days at 4° C.
Injectio	Calcium Penicillin 12.5 mega-units
Penicillini	White beeswax .. 4.5 grams
Oleosum	Arachis oil to 100 cc.
	Keeps six months at cool room temperature. Warm to blood heat and withdraw dose by warm syringe with intravenous needle. Does not suffer from up to a dozen warmings.
Cremor	Calcium Penicillin or
Penicillini	Sodium Penicillin 50,000 units
Sterilisatus	Lanette Wax SX .. 7 grams
	Hard paraffin .. 5 grams
	Liquid paraffin .. 41 grams
	Sterile water .. 45 cc.
	Keeps seven days at 4° C.
Cremor	The same, with 0.1 per cent. chlorocresol. Suitable for use by the patient.
Penicillini	
Unguentum	Calcium Penicillin, 50,000 units.
Penicillini	Ointment of Wood Alcohols, 100 grams. Keeps six months at cool room temperature. For use when grease is not contra-indicated.
Oculentum	The eye ointment contains 1,000 units per gram and no water, so keeps six months.
Penicillini	
Trochiscus	Each lozenge contains 500 units in about 1 gram of material. They last about four months at cool room temperature. They should be placed in the mouth outside the teeth.
Penicillini	

Unofficial Preparations

Eye Drops	1,000 units per cc. in saline. May be instilled every five minutes.
Insufflation	Calcium Penicillin in sulphathiazole, 5,000 units per gram for wounds, 500 units per gram for burns.
Powder	Calcium Penicillin 10,000 units per gram in glucose.
Snuff	NOTE.—Glucose attracts moisture.
Inhalation	80,000 units per cc. aqueous.