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PENICILLIN TODAY

'Case 1—Policeman, aged 43. Admitted Oct. 12, 1940. Suppuration of face, scalp and both orbits, starting from a sore at the corner of the mouth a month earlier. Primary infection *Staph. aureus;* secondary, *Strep. pyogenes.* Sulphapyridine 19 g. given from Dec. 12 to 19; no improvement; drug rash. Jan. 19: incision of multiple abscesses on face and scalp. Osteomyelitis of right humeral head, proved by X rays, showed on Jan. 31, 1941, after 3 weeks of pain; a resulting arm abscess, incised, gave *Staph. aureus* pus. General infection of left eye; cornea perforated Jan. 21. Eye eviscerated Feb. 3. Blood transfusion 2 pints Feb. 9. Fever intermittent all this time, 98°—101° F. Very ill and emaciated; tongue heavily furred. Feb. 11: right eye bulging and conjunctival chemosis, orbit incised, pus gave *Staph. aureus* and *Strep. pyogenes.*

'Feb. 12: all incisions suppurating, in scalp, face, both orbits and right arm. Lungs involved, with purulent expectoration containing both the pyogenic cocci. Hb 36%; reds cells 1,800,000. Blood-culture sterile. Penicillin 200 mg. given intravenously; then 100 mg. 3-hourly, intravenous except for two intramuscular doses. Slight rigor after first dose, otherwise no reactions. Striking improvement after total of 800 mg. penicillin in 24 hours . . .'[1]

This laconic report was the first announcement of the clinical use of penicillin. The circumstances were more dramatic than anything yet conceived by playwright or novelist. Britain was reeling under the savage blows of the Nazi aerial bombardment and there was death and destruction all around. While the machines of war were roaring overhead, two refugees from Nazi Germany, Chain and Abraham, together with a team of British scientists directed by Howard Florey, were working patiently and systematically in a small Oxford laboratory to extract a therapeutic principle from mould. Nearby, in the Radcliffe Infirmary, their clinical colleagues kept a close watch on the progress of the patients on whom the new medicine was being tested. 'Albert A.', the policeman referred to as 'Case 1', did not recover: after five days the supply of penicillin was exhausted and although he remained well for 10 more days, his condition then deteriorated until he died on 15 March 1941 from staphylococcal pyaemia with multiple abscesses. But many other patients did recover, and out of the holocaust of war emerged the remedy which may prove to be one of the greatest therapeutic blessings which has yet been bestowed on mankind.

It is only when one reads the early case reports that one realizes just how much the practice of medicine has been changed by penicillin. Little more than two decades ago, the simple pyogenic bacteria were responsible for some of the most ghastly deaths among young and old alike; syphilitic disease progressed with an awful inevitability despite the desperate use of highly toxic arsenical compounds; bacterial endocarditis was almost invariably fatal. Great changes were brought about 20 years ago by the first Penicillin Revolution, but recently there have again been great happenings, and it may be that a second Penicillin Revolution has already started, with the production of the synthetic penicillins. It is therefore appropriate at this stage to review the present status of penicillin therapy.

The original preparations of penicillin were impure and produced considerable pain when injected hypodermically. When they were administered intravenously, pyrexial and other systemic reactions often occurred. The first essential development was the purification of the crude extract and, of the several active constituents which were isolated, **benzylpenicillin** (penicillin G) has proved to be the most useful, producing little local discomfort when given intramuscularly. It is soluble and is rapidly excreted by the renal tubules, so that effective blood levels cannot be maintained for long and the injection has to be repeated every four to six hours. Despite this, benzylpenicillin remains the penicillin of choice in severe, acute infections caused by the common pyogenic cocci.

Several attempts were made to prolong the activity of benzylpenicillin. It was shown that the simultaneous administration of probenecid inhibited tubular excretion of penicillin, and this device is still useful when high blood levels have to be maintained for a long time: for example, in bacterial endocarditis. The combination of penicillin with aluminium monostearate was popular for some time, but now the procaine salt of benzylpenicillin — **procaine penicillin** — is the recommended preparation; it is effective when given by intramuscular injection once or twice daily. Effective blood levels can be maintained even longer with **benzathine penicillin**; for low-grade infections, two or three injections of 600,000 - 1,200,000 units at intervals of three to four days being all that is required. In practice, benzathine penicillin is usually combined with benzylpenicillin and procaine penicillin ('bicillin') so that a prompt as well as a sustained effect is achieved. In most cases of syphilis, four weekly injections, each of 1,200,000 units of benzathine penicillin, seem to be quite adequate.

Benzylpenicillin cannot be given by mouth because it is unstable in acid media. Considerable efforts were directed at the production of acid-resistant penicillins, and a number of reasonably successful compounds are now available. Of these, **phenoxymethylpenicillin** (penicillin V) is deservedly the most popular. It may be used with impunity in most mild and moderate infections caused by penicillin-sensitive organisms, the dosage being 125 - 250 mg. four times a day. Its most valuable application is in the long-term prevention of rheumatic-fever recurrences, and for this purpose it need be given only twice daily.

Even before penicillin was introduced into clinical practice, Abraham and Chain[2] showed that certain organisms produce an enzyme, penicillinase, which destroys penicillin. Most important are the penicillinase-producing strains of *Staph. aureus,* which are responsible for infections that do not respond to ordinary penicillin therapy. The extensive use of penicillin has resulted in the 'natural selection' of these penicillinase-producing staphylococci

and, particularly in hospital practice, there has been a dreadful increase in the incidence of septicaemia, pyaemia and enterocolitis caused by these organisms.[3,4] All sorts of manoeuvres were suggested to combat this menace, but none was really successful until 1960 when British scientists made another important advance by developing a practical method for the large-scale production of 6-aminopenicillanic acid.[5] This substance is the active nucleus of penicillin, and by varying its side-chain, penicillins with different properties can be synthesized.

Among the many new compounds that have been investigated are a group of penicillins which are not affected by penicillinase and are specifically useful in resistant staphylococcal infections. The first of these to become available was **methicillin** ('celbenin'). It is unstable in acid media and rapidly excreted, so it has to be given by intramuscular injection every four to six hours. The injections are highly effective, but painful, and it is not a pleasant drug to use. The more recent isoxazolyl penicillins are resistant to both penicillinase and acid and are effective when taken by mouth. Two of these are now available: **oxacillin** ('prostaphlin') and **cloxacillin** ('orbenin'). The usual dose is 500 mg. every four to six hours. More is known about the clinical use of oxacillin[6,7] than of cloxacillin,[8] but there is some preliminary evidence that cloxacillin is the better absorbed and may be preferred.[9] In severe infections it may be safer to give these isoxazolyl penicillins by intramuscular injection.

From the published reports it is clear that these new penicillins have already saved many lives. On the other hand, there are already rare examples of staphylococci resistant to methicillin,[10] and the possibility of resistance developing to oxacillin and cloxacillin cannot be excluded. It should also be pointed out that these new penicillins are not as active as the older penicillins against most penicillin-sensitive organisms. Accordingly, it is urged that *their use be restricted to clearly established cases of resistant staphylococcal infection, and that they should not be prescribed promiscuously for infections with other organisms.*

The introduction of synthetic penicillins has opened up exciting new vistas of antibiotic therapy. Theoretically there is almost no limit to the different varieties of penicillin that can be produced. Two main lines of development can be anticipated. Firstly, there is the production of penicillins of limited antibiotic range, but highly active against specific organisms. The penicillinase-resistant penicillins are the prototypes of this line and, taking it to its extreme conclusion, one can foresee the day when specific penicillins will be available, made to order, for specific infections. Secondly, penicillins with an increasing antibiotic spectrum are being developed. One of these, **ampicillin** ('penbritin'), is already available[11] and is effective by mouth against several kinds of gram-negative bacilli which had so far been unaffected by penicillin therapy. These include *H. influenzae*, salmonella and shigella species and some strains of proteus and *E. coli*.

Only one question-mark casts its shadow across the bright prospects of penicillin therapy: the question of hypersensitivity. The penicillins are remarkably free from toxic effect and can safely be given in advanced renal and liver disease and in the presence of blood dyscrasias. But a substantial number of patients are allergic to penicillin and this allergy may show itself as a mild systemic reaction, the development of acute and chronic skin reactions, or catastrophic anaphylactic shock. This antigenicity is shared by all the penicillins, and probably resides in the fundamental 6-aminopenicillanic acid nucleus; it is difficult to see how manipulation of the side-chain is going to alter this property. If, however, sensitivity reactions can effectively be eliminated, then the ideal of a *therapia magna sterilisans* will be close indeed.

But, of course, there will still be the viruses to contend with.

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DIE STERWENDE HART VERAL TEN OPSIGTE VAN NARKOSE

'. . . Toe alles klaar was, huis en dam en sloot,
Toe gaan ek dood.' (Eugéne N. Marais.)

Wanneer die dood naby is, as gevolg van watter oorsaak ook al, toon die elektrokardiogram dikwels wye mismaakte uitwykings en stadige idioventrikulêre ritme òf van enkele òf van politopiese oorsprong. Hierdie patroon word vandag kenmerkend genoeg geag om die begrip van ‚die sterwende hart' as 'n nuttige kliniese begrip te kenskets. Dieselfde toestand tree gereeld op nadat ventrikulêre stilstand of fibrillasie vinnig en suksesvol behandel is. Maar al te gou tree 'n agteruitgang in, gekenmerk deur progressiewe verwyding van die QRS-uitwyking, wat op sy beurt dui op vertraagde intraventrikulêre geleiding, die spoed van die hartslag neem af, en bondeltak en totale atrioventrikulêre blok en sinus-arres met 'n nodale of idioventrikulêre pas-aangeër tree te voorskyn. 'n Wye sine-golf kan nog vir 'n geruime tyd na kliniese dood by geleentheid waargeneem word.

Ten spyte van so 'n verloop is dit dikwels tog 'n geval van 'n hart wat eintlik ‚te goed is om dood te gaan'. So 'n geleentheid is nie baie seldsaam in die narkose nie.[1] Die narkose-toestand self, sowel as chirurgiese ingrepe, stel sekere eise aan die gestel. Dit is onlangs baie duidelik geopenbaar deur die bekendste Amerikaanse kliniek, sovêr dit navorsing in die narkose aanbetref, dat onder 16,000 funksioneel-gesonde pasiënte wat narkose met spierverslappers ontvang het, daar nie 'n enkele sterfgeval aan die

narkose toegeskryf kon word nie. Maar in pasiënte naby die dood is een uit sestien wat spinale analgesie ontvang het, dood as gevolg van hul narkose, en een uit tien is oorlede *as gevolg van die algemene narkose wat aan hul toegedien moes word.*[1] Hierdie studie weerlê dus die bewering van Beecher en Todd[2] dat spierverslappers 'n inherente sterftesyfer meebring, sowel as die huidige vrees t.o.v. spinale analgesie. (Meer as 16,000 gesonde pasiënte het almal hul spinale narkose sonder moeilikheid oorleef.)

Maar selfs die ‚sterwende harte' kan vandag dikwels gered word. Die eerste stap is om die miokardium van suurstof te voorsien. Wanneer ventrikulêre kontraksie nie 'n genoegsame druk in die aorta kan handhaaf nie, moet die bloedstroom in stand gehou word deur die ventrikels met die hand saam te pers. Veral wanneer bloedverlies die ventrikulêre ineenstorting veroorsaak het, help dit om die aorta distaal tot die boog te beklem totdat genoeg druk bewerkstellig is om die koronêre vate goed te vul. Hiernaas is die mees nuttige kunsgreep die binne-aarse toediening van natriumlaktaat, iets wat dikwels spesifiek is in die behandeling van intraventrikulêre blok.[3] Wanneer 'n vinnige drup-spoed van molaar natriumlaktaat onvoldoende was, het 'n 2·5 molaar laktaatoplossing die gewensde vernouing van die QRS-uitwykings teweeggebring, al het dit soms 250 ml. van 'n 2·5 molaar natriumlaktaat geverg binne die bestek van vyf tot tien minute.[4]

Noradrenalien, vireers slegs 4 mg. in 500 ml. 5% glukose in water, is altyd nuttig om hipotensie te bekamp. Dit is egter veel meer doeltreffend om 'n pressor-effek te bewerkstellig wanneer dit in 'n alkaliese milieu soos natriumlaktaat kan werk, as wanneer dit onaktief gemaak word in die suur milieu wat altyd volg op anoksie. Elektriese skok moet steeds beskikbaar wees om ventrikulêre fibrillasie te bekamp. Middels wat wel met welslae toegepas is, sluit binne-aarse kinidien,[5] kalsiumglukonaat, adrenalien, isopropylarterenol, en magnesium soute in, maar hul resultate is nie so standvastig as met die bogenoemde metodes nie. Noradrenalien en natriumlaktaat is soms nodig vir dae en selfs weke; hidrokortisoon help ook soms in die instandhouding van 'n pressor-reaksie, en digitalis is dikwels aangedui vir hartversaking.

Hierdie feite beklemtoon die absoluut onontbeerlike elektrokardiografiese kontrole wat gedurende narkose uitgeoefen moet word oor pasiënte wat nie heeltemal gesond is nie. Dit is die verbasende gebrek aan sulke maatreëls (wat baie jare reeds as vanselfsprekend in die universiteitshospitale oorsee aanvaar is) wat onlangs die wêreldberoemde prof. W. W. Mushin aangespoor het om die narkose in Suid-Afrika te kritiseer en daarop te wys dat ons glad te min navorsing op hierdie nuwe maar dinamiese en allerbelangrikste vakgebied van die moderne geneeskunde doen.

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