Technology 1940/1945

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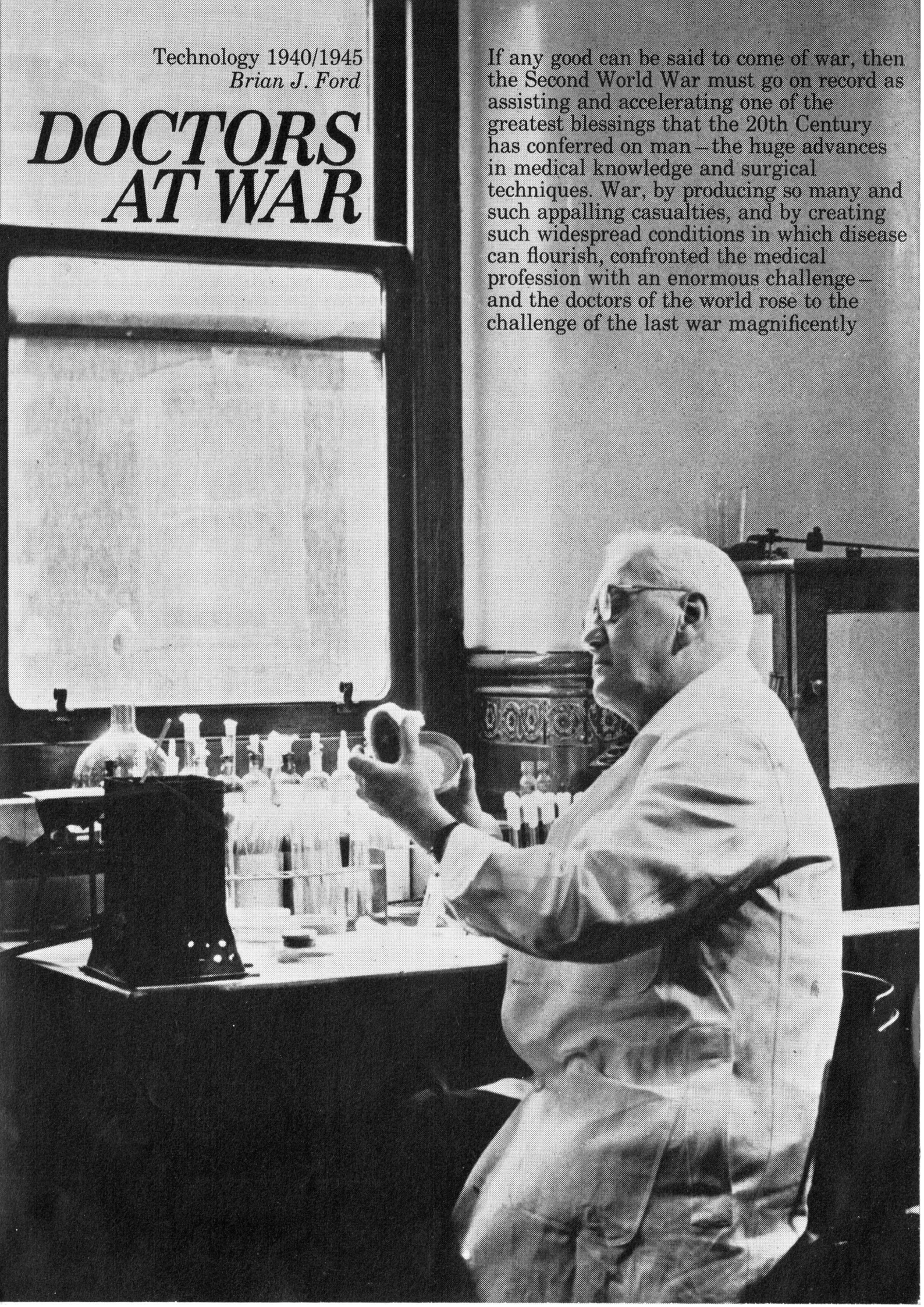
DOCTORS AT WAR

If any good can be said to come of war, then the Second World War must go on record as assisting and accelerating one of the greatest blessings that the 20th Century has conferred on man – the huge advances in medical knowledge and surgical techniques. War, by producing so many and such appalling casualties, and by creating such widespread conditions in which disease can flourish, confronted the medical profession with an enormous challenge – and the doctors of the world rose to the challenge of the last war magnificently



Keystone

Preparing penicillin cultures. Fleming's work on the drug was limited to small-scale laboratory tests, and it took many more experiments before the Glaxo Laboratories overcame the obstacles in the path of mass-production

The war revolutionised many fields of medical research and practice, creating advances which have been carried forward into peacetime. Perhaps the most important of these 'revolutions' took place in the treatment of infection, a revolution which began as early as 1936 with the development of 'M & B', one of the first uniformly successful drugs that could be used against infection without danger to the patient.

In 1936 work began at the Dagenham works of May and Baker Ltd on the structure and synthesis of sulphonamides, which had been developed by workers on the Continent (including medical research workers in Germany) some years before. A whole range of allied chemical molecules were synthesised in the laboratory, and were recorded in a research 'log' in numerical order. The 693rd compound to be uncovered in this way, sulphapyridine, was synthesised in the laboratory in November 1937. A sample of it was sent for testing to Dr Lionel Whitby, at that time a pathologist at the Middlesex Hospital, who inoculated mice with pneumococci (the organisms that produce severe pneumonia) and then gave them sulphapyridine. They lived. Sulphapyridine was tested in the laboratory against many other infective agents, ranging from those that cause sore throats to those that produce gonorrhoea. The drug killed all of them.

In this way sulphapyridine became (under the name 'M & B 693') the first really effective drug against bacteria and, for the first time in history, a useful chemotherapeutic agent against pneumonia. In 1938, with the shadows of war looming steadily closer, another sulphonamide called sulphathiazole was discovered and given the name 'M & B 760'. With the declaration of war, May and Baker—like all chemical and pharmaceutical firms—were called upon to redouble their efforts. Large quantities of the M & B drugs were produced, and indeed Winston Churchill himself referred to the drugs in a 'message to the nation' broadcast on December 29, 1943. He had just recovered from pneumonia, and stated: 'This admirable M & B, from which I did not suffer any inconvenience, was used at the earliest moment and after a week's fever the intruders were repulsed.'

The German scientists were similarly preoccupied with chemotherapeutic agents, and developed 'Marfanol' to this end. The Russians, in turn, developed 'Streptocid', their own chemotherapeutic agent.

May and Baker were busily occupied by now in other branches of chemical manufacturing; their methyl bromide was developed for use in fire extinguishers with which every aircraft in the RAF was eventually equipped. Photographic chemicals too were necessary, as well as anti-malarial drugs. Other firms produced such materials, too, and in vast quantities; DDT came into its own as a controller of the insect vectors of typhus and scabies.

Without question the most famous—indeed, almost legendary—wartime development was the production of penicillin. The original discovery, the story of Fleming's original observations, is well known. Suffice it here to say that the original observations took place in 1928, when Fleming—carrying out routine culturing techniques involving the growth of *Staphylococci* at St Mary's Hospital, Paddington—observed on one of the plates an intruder: a small colony of a greenish fungus, much the same as that seen on decaying matter and on blue-vein cheeses. What was odd about this one was that the colonies of bacteria near the fungus growth were dying off. Something, secreted by the fungal colony, was capable of destroying the growth of harmful bacteria.

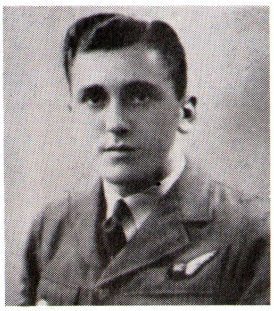
The material concerned proved to be penicillin—but the species of fungus was not (contrary to what is generally believed) a new discovery itself; it proved to be *Penicillium notatum*, and had been originally discovered by Westling in 1911, when he cultured it from decaying hyssop in Scandinavia—though there was no indication of the overwhelmingly important effects that it was going to have on world medicine in due course.

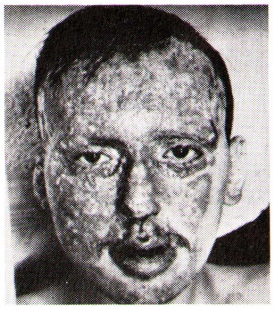
Sir Alexander Fleming did not carry the discovery of penicillin very far. He carried out some small laboratory tests, but that was all. It is to the efforts of a now largely forgotten scientist, Dr H. Raistrick, that we owe the development of penicillin as an antibiotic—in a race against time that was run throughout much of the war period.

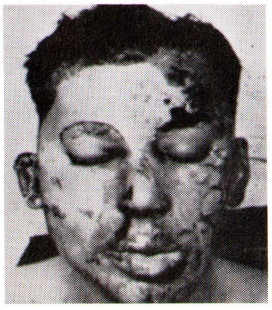
A forgotten man

Raistrick had, in 1932, investigated something of the chemical properties of penicillin. But, try as he might, he could arouse no interest in his discovery: as a contemporary wrote of him: 'His medical colleagues would not listen to his pleadings and he could get no clinical tests made.' It was not until the war years that production techniques got under way at last, and Raistrick (though he is virtually a forgotten man today) was closely associated with most of this crucial research.

It was in 1941 that, in an effort to find drugs for the wounded, penicillin came up for

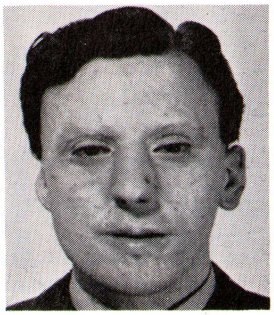


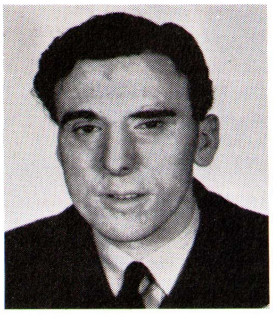




Camera Press

▽ Filatov, Russian inventor of the 'walking stalk' skin graft operation. △(*Left*) 'Archie' McIndoe, the great British plastic surgeon. The sequence of photographs at right illustrates the progress of one of McIndoe's most successful cases of facial repair





Camera Press

Queen Victoria Hospital

consideration once again. There were many important developments that had to be made: for example, the penicillin then known was available only in small yields from the culture medium; the active material itself was unstable, and soon became useless; and the separation of the antibiotic from the fluids from which it was extracted posed further great problems. At the beginning of the war the yields obtained from the liquids on which penicillin-producing moulds were grown were only about 3 milligrams per litre of solution. How powerful, then, the drug must have been in order to exert its deadly bacteriostatic effects even when so diluted!

The antibiotic itself was extracted by running the broth, on which the *Penicillium notatum* had been growing, through activated charcoal; the penicillin was adsorbed on to the surface of the carbon. Then treatment with water mixed with various organic solvents served to release the antibiotic from the charcoal, so that it could be further purified.

It was at the Glaxo Research Laboratories in Middlesex that the research pressed ahead; by now it was a question of biochemistry and technique, and two experts in these fields, Dr B. A. Hems and Mr A. L. Bachrach, carried out an intensive period of 'crash' development in an attempt to produce sufficient quantities for the medical needs of the wounded and diseased in the war.

The first problem was to stabilise the compound, best done in many instances by the production of a sparingly soluble metallic salt of the drug—but here too penicillin proved awkward to handle. Many metallic ions, such as iron, zinc, copper, mercury, and lead, were all capable of inactivating the material, rather than potentiating it and enabling it to remain stored for long periods. In fact, after a protracted research programme the metallic salt which was being sought never materialised.

But large-scale production was still the biggest problem. And not only in this country, but in the USA too, scientists turned to tackle it. Crude penicillin—having an activity of 40-150 units per milligram, the unit being an accepted rating of potency against harmful bacteria—was easily obtained; but how to extract the drug in bulk? Many procedures were tried: virtually every conceivable approach was investigated during the early war years. The answer, it was found, lay in chromatographic separation: the liquid was allowed to percolate through a tall column of aluminia and, after treatment with different solvents, the penicillin was picked up by a narrow zone of the column and was adsorbed on to the surface of the aluminia. Later an improved technique, known as partition chromatography, was evolved, and in this way the extraction of large amounts of the drug became feasible.

At about this time, before any of the pure penicillin itself had ever been crystallised, some interesting clashes of interpretation arose between the British and American scientists. Each side felt inclined to imagine that the other had included some impurities which were changing the concept of the drug itself, but with the careful use of partition chromatography—which enabled the detailed constituents of the fluid mixture to be accurately distinguished—the truth suddenly dawned; there were two penicillins.

Now a new field of investigation opened up: why were there differences, how did they

arise? And – perhaps most interesting – which form was the best penicillin? Within a year or so a whole range of penicillins had been discovered, produced by slightly different strains of *Penicillium notatum* in some cases, or due to the incorporation of different food materials in the culture media in others.

Large-scale production got under way with the growth of the fungus in containers mounted in large racks – milk bottles were used in one stage of development for the production of penicillin for the troops. In production there were, once again, several important factors that had to be met: it was important to encourage the highest possible level of production of the antibiotic in the nutrient broth on which the fungi were grown, and from the experimental yields of perhaps 10 units per millilitre of the culture fluid in the earliest experiments, this was raised to 50 for the first large-scale production – and to 200 by the addition of 'corn steep liquor'.

This miraculous leap in potency was made possible by adding to the broth of this fluid a waste material produced by maize cultivation. The exact nature of the growth-stimulating agent was not clear, but by the end of the war all penicillin production included this interesting and important additive to the culture medium. As a result, from the early forms of penicillin, it was possible to increase the potency of a given weight of the extract by 20 times; and to produce 1,000,000,000 units of the antibiotic, only 2,000 gallons of culture medium were needed, instead of the earlier 56,000 gallons – a marked improvement, and in the event an important aid to large-scale production.

A costly new process

Even so, the method of production was time-consuming and difficult. There was always the possibility of including micro-organisms that produce *penicillinase* (an enzyme that destroys the drug) and so a good harvest could be reduced to nothing literally overnight. Careful handling and inoculation kept the risk to a minimum and large numbers of women workers were trained to distribute the medium into bottles or flasks, shown how to keep the contents free of contaminants, and then how to remove the liquid for processing – a liquid containing perhaps as little as 0·01% of the penicillin!

But the whole principle of production in this fashion is wrong: to extract large quantities of a metabolite like penicillin (that is to say, a chemical produced by the growth and the life-activities of an organism) something more continuous is necessary, rather than the separate handling of thousands of separate containers. In 1942 the American researchers began to investigate the problem of large-scale production in vats, instead of bottles. Their research results were all transmitted back to Britain, but it was apparent to the workers at Glaxo and elsewhere that Britain could not finance the development of such a new and costly process. So the Americans pressed ahead, and by 1944 had begun pilot production of the antibiotic by the new, deep-fermentation process. Now, by the use of *Penicillium chrysogenum* (a closely related organism to *Penicillium notatum)* mass production in the true sense became possible, and it was at the end of the war, in 1945, that a deep-fermentation unit was installed in Barnard Castle, County Durham, for the first large-scale mass production of deep-fermentation penicillin in Britain.

Even so, the Glaxo factory had been able to produce vast amounts of the penicillin by using the cruder separate-container technique. Some 80% of the British-made supplies for the invasion of 1944 were produced in this fashion by the company.

Penicillin came into battlefield use during the middle period of the war, but only in small quantities. And although it was at

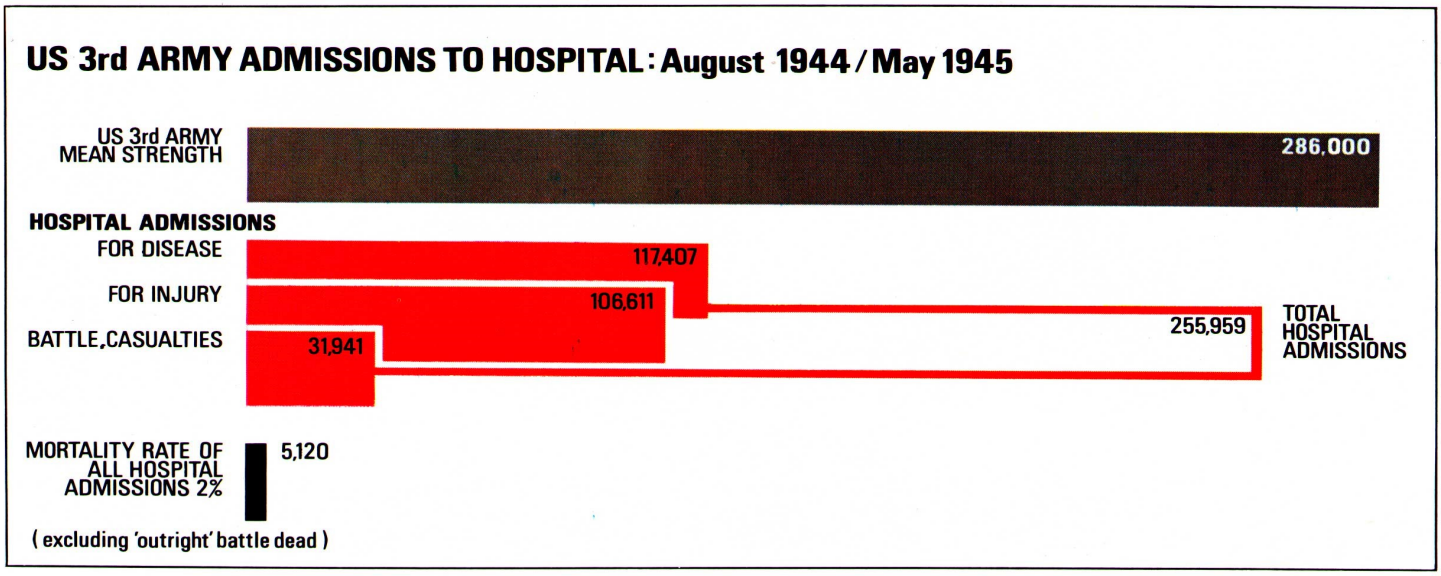
Large-scale production gets under way. *Above:* Flasks of culture medium in the early stages.

this time used to *treat* infections, experts felt it was time to begin using it to *prevent* infection, as well. But it was not until the invasion of north-west Europe that there was enough of the antibiotic available for both prevention and therapy. After D-Day, the whole system of penicillin use in the 21st Army Group was based on prevention and therapy – and well over 100,000 men were treated with the 'wonder drug' during that campaign.

The antibiotic proved to be effective against a wide range of the most troublesome bacteria which earlier claimed the lives of the wounded, and it was soon adopted for use in all severe wounds. After the wound had been cleansed and sutured, the adjacent area was dusted with penicillin powder (for economy, it was made with 5,000 units of penicillin mixed with every 1 gram of sulphonamide) and injections of the drug were given too. To prevent the chance of a partially-cured infection flaring up in penicillin-resistant form, treatment was continued until the army surgeon recommended that it be curtailed, and men were given injections of up to 100,000 units immediately after being wounded – or as promptly as possible – and then further 'shots' of 50,000 units every five hours thereafter. This was in many ways an extravagant way of doing it – but the strategy was wise, and it meant that any error of dosage would be on the right side of the line. (Penicillin overdosage was, and is, virtually impossible.)

Reports flooded in from all sides: the penicillin was working wonders; infections were dramatically cut to a small fraction of their previous levels – and, notwithstanding the pessimists who pointed out that improved surgery, better communications, and the like played their part, it was clear that the greatest measure of improvement had – undeniably – been due to the use of the antibiotic. In the Middle East forces, infection with *Streptococci* were most common,

The US system: high admissions, low mortality



clostridial infections (similar to gangrene) running high too. In the British forces in Europe, on the other hand, *Staphylococci* topped the list with *Streptococci* and *Clostridia* much further down; yet, in spite of these very different patterns of infection in the field, the antibiotic brought about improvements.

Conditions in the field were often appalling, and the success of the drug has to be weighed against the daunting factors mitigating against recovery – for instance it took an average of about 14 hours for a soldier to be brought in for surgery after being wounded, a time-lapse that did not vary significantly throughout the whole of the Middle East forces, the British forces in Europe, and the Central Mediterranean force. An analysis of the period October 1944/March 1945 showed that in the 21st Army Group, 1,300 men had their wounds sutured by the surgeon between one and seven days after wounding, and over 850 had to wait for eight days or more. Many of them had penicillin-treated dressings during the period, and in spite of the poor conditions for many of the wounded, the saving in life continued apace. There were difficulties, of course: sometimes an impurity in the drug itself caused a rise in temperature; in other instances an infection (such as osteomyelitis) would be masked by the antibiotic, only to flare up – sometimes in an incurable state – as soon as treatment was stopped. However the overall revolution in treatment was vital to the war effort, and has been of great significance in peacetime medicine as well.

Hope for the hopeless

Perhaps next on the list of important wartime developments came plastic surgery, and the art of repairing severe wounds. Here too important advances were made in all countries concerned, by the very virtue of necessity. Some transformations in technique were dramatic and important, and many badly wounded men were able to be treated who in peacetime might have been passed over as beyond hope. Burn victims were one example of apparently hopeless cases who were returned to a normal life.

It was (to take just one example) the Russian Filatov who made one such important development: the 'walking stalk' operation. It is a masterpiece of surgical thinking, and proved to be a progressive step.

This technique involved the development of skin grafting, which had tended to fail when the transplanted area of skin failed to 'take' on its new site. Filatov found that it was possible to detach a segment of skin along three sides of a rectangle, leaving it attached at one end. The detached portion was then rolled into a tube and sutured in that position. Meanwhile the segment was looped over towards the damaged area of the body that required the graft, and it was then secured in that position until it had properly 'taken root', as it were. The other end was later detached, looped across in head-over-heels style, and secured once more to the body. In this way, with a period of several weeks between each manoeuvre, it was possible to 'loop' a segment of skin across the body from one region to another, in such a way that it never lost contact with the tissues that nurtured it. Finally, when it was on site, the cylinder was opened flat and the skin sutured into its new position.

Other surgeons carried out dramatic operations in which limbs were repaired after being severely damaged; new tongues were even made and stitched into position with success; and damaged nerve trunks were encouraged to regenerate. The advance of surgery was many-sided and profound.

During the war years the Russians also carried out a branch of research peculiar, in many ways, to their own medical investigators: the search for 'biogenic agents' which would encourage healing and regrowth of damaged areas. Shortly before the war they found that a chemical produced by ordinary beans – 'traumatin' – would have such an effect. Analysis showed it was nothing so dramatically unusual, in chemical terms; it turned out to be dicarboxylic acid. Other related compounds were unearthed from unlikely sources, including conserved fish liver (which contains oxalic acid and succinic acid) and preserved aloe (containing cinnamic and lactooxycinnamic acids). Soviet doctors developed these and used them in the treatment of the wounded.

As an ancillary aid to the surgical and medical treatment of wounds, the blood transfusion service generally developed from a more-or-less primitive and experimental medical expedient into a large, well-organised service. It was in 1940 that the rhesus factor – Rh – was discovered, so completing the basis of understanding on which the discipline of transfusion could develop. It was during the early stages of the war that the first blood banks were instituted – although in the First World War there had been some attempts at storing blood for transfusion, but the practice had been ignored until interest was revived by the Spanish Civil War. In the 1940s the routine cross-matching and storing of blood became widespread. The blood bank service as we have it today largely resulted from this enterprise.

It was through studies of the blood that malaria – for many years a mystery, since the malaria parasite was known to disappear from the bloodstream after its introduction through a bite by an infected mosquito – began at last to be understood. Sir Neil Hamilton Fairley, using Australian soldier volunteers during the war, investigated the problem in some detail and paved the way for the final identification of the life-cycle of the parasite in 1948 by Shortt and Garnham. DDT was widely used to destroy the mosquitoes that transmitted the malaria or-

ganisms, and in 1942 Fairley and his co-workers showed that soldiers in the South-West Pacific area could be kept free of malaria by taking one tablet of mepacrine per day. This drug had actually been discovered by German scientists in 1933, when they christened it atebrin; it was the successful outcome of a programme of research in which more than 12,000 compounds were synthesised and tested—an impressive total by any standards. Other anti-malarials produced by the spur of war included paludrine (in the British Isles) and chloroguanidine (synthesised in the USA). By the outbreak of war German research workers had pressed still further ahead with the production of chloroquin, an even more advanced drug. They were not obliged to use a great deal of the material, of course, since it was mainly a standby for tropical action in which German forces were not, to any extent, involved.

Tetanus had also been a dangerous disease of wounded men in earlier wars, and that too came in for some active attack in the war years. Tetanus organisms develop only in badly lacerated wounds where there is no oxygen (these anaerobic organisms are actually poisoned by traces of pure oxygen), and so they are an inevitable consequence of war wounds. In addition it is important to point out that because the micro-organisms live normally in soil, soil-contaminated wounds are always likely to give rise to this often fatal disease.

Another great life-saver

Active immunisation of the soldier against tetanus was introduced before the war, based partly on the findings of the doctors who had administered anti-tetanus serum to soldiers wounded in the First World War. At the beginning of that war, nine soldiers out of every 1,000 wounded would develop the disease, but after they were given prophylactic 'shots' of the serum the number fell to one in every 2,000. Sir John Knox Boyd, who studied the effects of immunisation in the Second World War, found that it was almost entirely successful. For obvious reasons it was not possible to administer serum to the wounded at Dunkirk, but because they had all been given immunisation treatment before leaving England there was—out of some 17,000 wounded men—not one single case of the disease (in a sample of less than 2,000 men who had *not* been actively immunised the total of cases was eight). As the war dragged on, similar results continued to occur, although there were sporadic cases even among those who had been actively immunised in this way. However, the saving of suffering and disability—and of life, too—was great.

Of course the terrible social consequences of war reap their harvest of disease too. Many diseases showed a tendency to increase during the war years, particularly tuberculosis, which showed the first turn upwards in the graph for many years. Why this should have been is not clear: certainly malnutrition played its part, but the isolation of those concerned and the postwar development of antituberculous drugs (such as PAS) have been instrumental in cancelling out the bad effects of this wartime setback.

A great deal of research was carried out into an important form of medical development which, as it happens, was never needed on the scale that had been feared: the protection against medical, biological, or chemical attacks by the enemy. Both German and Allied research into the problem was active at the beginning of the war, but it was the research in the USA which—while representative of the rest—was by far the most developed and so, to illustrate this important aspect of wartime research, we will examine what happened in America.

Many of the predicted problems were similar to those of peacetime health research: phosgene injury, for example, is much the same as pneumonia and is treated in a similar manner; and the burns of the mustard-type vesicant gases are treated similarly to those resulting from direct heat. But there were few startling defensive aids for the soldier at the beginning of the war; the position was much the same as in 1914.

Lung damage through phosgene poisoning produces an oedematous swelling that can only be cured by time. The problem therefore is to keep the patient alive long enough for the lungs to recover of their own accord. This entails flooding the lungs with oxygen, and apparatus to do this was perfected in 1943 and went into production a year later. It was not, of course, needed in the war effort as such, although it was later adapted for use in civilian hospitals.

Damage from mustard gases was twofold: pneumonia and surface burns. The pneumonia was often fatal, but that in the war could have been controlled by penicillin and the sulpha drugs. The burns caused to the surface of the skin were less likely to kill, but they remained open for many months and caused great pain and inconvenience. An ointment, called M5, was eventually developed which, applied to the skin before or shortly after the mustard, controlled the damage by neutralising the poison.

Another important development in this branch of medical research was a British discovery, DTH. It was found to be effective in preventing the burns and arsenical poisoning of lewisite, and the Americans took it over for further development and production. They named it BAL (British Anti-Lewisite) and it was made up as a skin ointment. The Du Pont laboratories produced it in quantity, first as a liquid but eventually as an ointment which was easier, in practice, to apply to the eyes than were eyedrops. More important, it was found that BAL is effective against arsenical poisoning in a more general sphere, and this too has come in for civilian use.

It was even possible to find an antidote to cyanide gassing. Hydrogen cyanide and cyanogen chloride were both tested, and it was found that cyanogen chloride is—though virtually as toxic—less dangerous to the soldier. This is because he can, if he remembers, always hold his breath and run to an uncontaminated area (at least in theory); the prussic acid gas, hydrogen cyanide, on the other hand, is more lethal since it is impossible to hold one's breath. An instinctive gasping response forces the victim to inhale still more of the deadly vapour. In addition, cyanide is odourless, unlike the cyanogen, and so is less likely to be detected until too late.

However, amyl nitrate was found to have a protecting effect against the cyanide. It appears to 'bind' the cyanide chemically, so that it is captured into an inert form, preventing the gas from producing its damaging effects. Amyl nitrate is still used against acute cyanide poisoning which may happen from time to time in industrial accidents.

As a result of this research, soldiers were kitted out with tubes of the relevant

Below: 10,000-gallon fermentation tanks, developed from American research and resources

agents, cream, ointment, and so on, and were also given pads soaked with copper sulphate solution, claimed to help in the removal of flecks of burning phosphorus on the skin. Above all, however (and this of course applied to the civilian population too), the development of gas-masks played an important part.

Updating the gas-masks

Gas-masks were of many forms. During the war years, the design and performance standards were continually revised wherever possible. A moulded rubber facepiece, first introduced in 1938, aided both comfort and security. However the rubber supplies were hit as the war progressed, and so alternatives were sought. Neoprene, now a widely-used plastic material, was first used for this purpose although in those days plasticisers were poorly developed and the synthetic plastic material had a tendency to become inflexible in cold weather. As a result a new substitute in the form of butyl rubber was found.

On the adsorbent side, many improvements were made to the carbon used to adsorb toxic gases from the inhaled air; a copper-impregnated, activated-charcoal compound was developed and found to be effective against phosgene, chloropicrin, mustard, and lewisite. Later the Americans developed a material known as whetlerite which was effective, in addition, against cyanogen chloride, arsine, and cyanide itself. Later developments were aimed at making the masks lighter, more portable, less obtrusive.

Most vulnerable of all were, of course, the wounded. In the event of attack they would be unable to move from their beds, in many cases, and of course head bandages would frequently preclude the possibility of wearing a gas-mask of conventional design. For them a special headwound gas-mask was evolved, which was able to cover the head entirely and still allow for the positioning of bandages. Other masks for animals were also designed, since mules and horses were not entirely obsolete in the war effort.

Finally some progress was made in one of the most insidious forms of attack – the use of micro-organisms in biological warfare. In the war there were occasional examples of this form of research being continued, although, in the words of a military biologist reported recently to have spoken in 1942: 'It is highly questionable if biological agents are suitable for warfare.'

Many bacterial toxins were almost certainly investigated at military research establishments which are still secret; in England research involved the testing of some agents probably of this nature on Scottish islands which today are still sealed off from outside visitors. The Japanese were rumoured to have dropped bubonic plague organisms, or fleas infected with them, in one or two small raids. But the biological war never materialised in any form: the delivery of such agents was difficult, and the chance of retaliation great.

So we can see the vast range of endeavour during the war years. Science in general, and medical science in particular, assumed a position of paramount importance. In contrast to many other scientific developments of the war, the advances in the field of medicine were, and are, of incalculable value to the whole human race.

[*For Brian J. Ford's biography, see Vol 3, page 1117.*]