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CHEMOTHERAPY OF TUBERCULOSIS

RESEARCH DURING THE PAST 100 YEARS*

BY

P. D'ARCY HART, M.D., F.R.C.P.

Scientific Staff, Medical Research Council

PART I

Viewed historically, the conception of treatment in tuberculosis has been as complex and as changing as in any branch of medicine. Emphasis on it as a social disease, a hereditary stigma, a contagion, an inflammation, or a bacterial infection has determined the approach to treatment and prevention. In the present lecture I shall attempt to trace the historical development of the chemotherapeutic aspect of tuberculosis treatment, so that the physician, more particularly the non-specialist, may be helped to see in perspective the successes which, if not already in the foreground of the future, are perhaps no farther away than its middle distance. I shall aim to present this development in relation, on the one hand, to the tremendous advances in general chemotherapy, and, on the other, to the advances in the broad knowledge of tuberculosis and of its management and treatment; and I shall attempt to weave into the complex historical pattern the development of the use of antibiotic substances.

First, I must make clear how I propose to use the term "chemotherapy." Most revolutionary concepts are not static, and chemotherapy in the sense of Ehrlich, who first coined the word, is no exception. Conceived by him as a science which "treats of the action and mechanism of the effects of chemical substances upon cells, and especially of drugs upon disease-producing organisms" (see Kolmer, 1926), it has been restricted by some to artificially produced chemicals and expanded by others so as to include the pharmacotherapy of non-infective disease. All agree, however, that chemotherapy is to be differentiated from therapy by means of immune bodies or such microbial products as tuberculin, and that it excludes the chemical treatment of symptoms. I propose to follow Galdston (1940) and keep in mind the *objective* of chemotherapy given by one worker: "to destroy the parasites in the body of the host, or at least so to injure them that they will prove vulnerable to the host's own defensive powers," taking this definition to cover bacteriostatic as well as bactericidal action, and to imply the proviso of relative harmlessness to the host. I shall include, therefore, consideration of antimicrobial agents that are inorganic substances, that are purely synthetic organic compounds, and that are organic compounds obtained from natural or biological sources—e.g., those products of microbial origin now known as antibiotics,† even though relatively few of these last have been isolated, purified, and characterized, and fewer still fully understood structurally. Divisions are rather artificial here, for what is obtained from biological sources to-day may be synthesized in the chemical laboratory to-morrow, and series of related compounds may be made the week after. Too precise a definition of chemotherapy is unwise, for, as originally visualized by Ehrlich in the strict sense, it involves complete internal disinfection in the living body with one or two doses; but Ehrlich himself allowed this interpretation to be widened as a result of experience. Again, Ehrlich undoubtedly conceived throughout his life the effect of chemotherapeutic agents as being produced primarily by direct and specific action upon the invading organisms—though the host's tissues might oxidize, reduce,

or otherwise convert an inactive drug to an active form. Yet there are instances where the action has been presumed to be wholly indirect—viz., stimulatory to the natural defensive mechanisms of the body (reticulo-endothelial system, etc.); such instances are properly regarded as examples of chemotherapy, and one of them—gold therapy—has been prominent in tuberculosis. Nevertheless it is true to say that the most successful recent efforts at specific chemical treatment can be explained on the basis of primary direct action of the agent on the micro-organisms.

The hundred years covered by the present review will, for convenience of discussion, be divided into four periods: 1850–80, 1880–1910, 1910–35, and 1935–46. The reasons determining these arbitrary divisions will be evident from Table I.

TABLE I

1850–1880
Pre-chemotherapeutic period—the background (A few traditional specifics of value in infective diseases—e.g., cinchona for malaria, mercury for syphilis)
1880–1910
Tentative period of chemotherapy (1890–1900) Period of first successes with synthetic substances (trypan red, salvarsan, etc.) in protozoal and spirochaetal infections (1900–10) Tubercle bacillus discovered (1882) Tuberculin discovered (1890) Unsuccessful chemotherapeutic experimentation in tuberculosis
1910–1935
First success with synthetic substance (optochin) in systemic experimental bacterial (pneumococcal) infection in man (1935) Chemotherapeutic tests with synthetic and natural substances in experimental tuberculosis negative or inconclusive Gold therapy in clinical tuberculosis flourished (1925–35)
1935–1946
First success with synthetic drug (sulphanilamide) in systemic bacterial (streptococcal) infection in man (1935) Sulphonamides in experimental tuberculosis (1938–46) Sulphone compounds in experimental and clinical tuberculosis (1939–46) Gold therapy for tuberculosis in decline First successes with antibiotic substance (penicillin) in systemic bacterial infection in man (1940–41) Streptomycin in experimental and clinical tuberculosis (1945–6)

1850–1880

The period 1850–80 was remarkable because the first foundations of modern chemotherapy were being rapidly laid, although success in this new branch of science, as a result of purposeful experiment and synthetic chemical search, was to come only later. Indeed, as Dale (1923, 1943) points out, there were few drugs of that time which, in the light of present knowledge, had remedial value due to action on the infective agents responsible for the diseases in which they were used—mercurials and iodides for syphilis, cinchona and quinine for malaria, and ipecacuanha for (amoebic) dysentery, to which we should probably add chaulmoogra oil for leprosy; and these remedies—triumphs of empiricism—antedated by some hundreds of years the discovery of the parasitic causes of their

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† An antibiotic substance may be defined shortly as a chemical substance produced by a micro-organism and found to be inhibitory to the growth or activity of other species of micro-organism (see also Waksman, 1945; Oxford, 1945).

respective diseases, and, in the cases of the biological products cinchona, ipecacuanha, and chaulmoogra, the elucidation of their active components.

In this pre-chemotherapeutic era we have the background of our subject. The most relevant of the many and exciting developments in science may be enumerated.

1. A phenomenal expansion of synthetic organic chemistry was accompanying the rise of the synthetic coal-tar dyestuffs industry. (This development was most prominent in Germany, due to the stimulus of economic demands and the lack of available natural products: yet it was an Englishman, Sir W. H. Perkin, who in 1856 prepared the first aniline dye (see Clegg, 1938).)

2. The science of human microbiology was being founded by the proof that micro-organisms could be factors in the causation and transmission of infectious diseases. Human diseases in which this was demonstrated included anthrax, relapsing fever, leprosy, gonorrhoea, and typhoid fever—but not yet tuberculosis. Pasteur and Koch were, of course, two of the giants in this field.

3. Pharmacology was ceasing to be a purely empirical subject, with the effects of drugs judged only at the bedside; and the advances both in synthetic organic chemistry and in physiology led to the union of these into an experimental science, and so to the study of the action of drugs on abnormal and artificially diseased animals—i.e., experimental pathology.

4. The selective staining properties of newly synthesized aniline dyes were being used by Weigert, Koch, and others.

5. Knowledge of local antiseptics was arising through the work of Lister and others; this advance, with phenol as starting-point in 1867, again illustrated how the influence of the distillation products of coal tar permeated the developments of this epoch.

In this pre-chemotherapeutic period, too, even the use of antibiotic substances in medicine was foreshadowed, for microbial antagonisms were first described in 1877 by Pasteur and Joubert, who had observed that the growth of anthrax bacilli *in vitro*, and the development of the disease *in vivo*, could be inhibited by certain air-borne micro-organisms; and these authors suggested that such antagonisms between different species might eventually have therapeutic applications.

As regards the advancing knowledge of tuberculosis, this period includes what Pagel (1927) has called the era of definite morphological investigation, arising out of Laennec's work and leading immediately into the period of experimental pathology and of the bacteriological study of experimental infections; thus we can see a thread running from Virchow's contributions to cellular pathology (1858), through Villemin's proof in 1865 of the specificity and transmissibility of tuberculosis, to Koch's discovery of the causative parasite in 1882. In the therapeutic field the principal measures recommended at this time were rest, sometimes tempered with exercise, and plentiful diet, often to the point of overfeeding, where the patient could afford it. The Brompton Hospital had been founded in 1848 and a sanatorium was started in Germany in 1859, but it was not till the end of the century that these methods began to be generally accepted; while fresh-air treatment was still a novelty to many and the rationale of isolation was disputed.

Among these general measures of treatment drugs found their place merely as one more weapon in the physician's armoury, and one which, perhaps wisely, many regarded as too blunt to use. There were, however, many others of whom Wells and Long (1932, p. 194) have written: "It was a time when a drug was seldom dropped, although it was a routine procedure to add one." Among the drugs there were quite an array which were commonly believed to strike at the root causes of tuberculosis and not merely at its symptoms—even though the bacillus was yet to be discovered—and their administration therefore deserves to be considered as an effort at empirical chemotherapy. These drugs were based largely on the traditions of the past, and showed little evidence of the impact of current advances in understanding of the pathology of tuberculosis. A patient of this time might have been treated with one or more of the following popular drugs in this class: (1) inorganic arsenical compounds, traditional for phthisis since antiquity (Hippocrates, Pliny); (2) tannin, an ingredient of anti-phthical medicaments known to Avicenna in the 11th century; (3) cod-liver oil in very large doses, this product having been prescribed for consumption in 1774 by Thomas Percival, but having probably been in use among fisherfolk much earlier; (4) iodine or iodides, which, in the form of sea-

weed, had been recommended for scrofula by the Salerno School in the 11th and 12th centuries; (5) mercury and gold, the use of both of which for phthisis and for scrofulous glandular swellings, as well as for syphilis, dates from the time of Paracelsus and Fracastorius, early in the 16th century; and (6) creosote, which had originated more recently, around 1830. In addition to these drugs of international popularity there were countless supposed specifics of indigenous vegetable origin in various parts of the world—e.g., garlic in the Ayurvedic and Unani systems of medicine.

Clearly the controlled experimental search for chemotherapeutic agents in tuberculosis had not yet begun. Moreover, unlike the use of the traditional drugs—ipecacuanha, cinchona, and mercury—in protozoal and spirochaetal diseases, subsequent experimental work has failed so far to show a definite scientific basis for success of any of the early empirical "specific" remedies in tuberculosis, with the possible exception of the ingredients of cod-liver oil. However, we should keep an open mind on this matter.

1880-1910

The 30 years 1880-1910 saw the establishment of chemotherapy as a flourishing branch of medical science, but (apart from antiseptics through local application) the bacterial infections remained resistant, even though the micro-organisms causing most of them had been discovered by the end of this period.

In the first part of the period—viz., the last two decades of the century—the foundations of chemotherapy were being strengthened and many of its tools fashioned. The expanding production of synthetic coal-tar derivatives was creating a pharmaceutical science. Many new dyes were being synthesized, the bacteriostatic and bactericidal action of some of them demonstrated, and their power of manifesting micro-organisms, both in isolation and in the tissues, through selective staining (e.g., acid-fast stain) exploited. Knowledge of immunology was being rapidly accumulated. The scope of the new experimental pathology was widening, attention being directed to the infective causes that were being discovered in one disease after another, including tuberculosis, with the implication that the ultimate objective of treatment should be to cure through the eradication of the parasites by the specific action of immune bodies or antiseptic chemical substances, and not merely to assist Nature by alleviating symptoms. Furthermore, current reports of the antagonistic power of certain bacterial species against others were opening up the therapeutic potentialities of chemical substances synthesized by micro-organisms themselves, thus bringing the anticipations of Pasteur and Joubert nearer. Ehrlich, greatly influenced by this complex of developments, to which he was himself a contributor, was paving the way for his great work in the theory and practice of chemotherapy by forming his conception of selective and specific chemical affinities.

First Experiments in Chemotherapy

But laboratory chemotherapeutic experimentation had already started, and it is interesting for our purpose that what was probably the first such experiment in animals, using a definite chemical entity—i.e., an attempt to produce internal disinfection in a systemic infection—was made by Robert Koch in 1881, a year before he announced his discovery of the tubercle bacillus. Koch's experiment—a test of mercuric chloride, which was very active against anthrax bacilli in the test-tube, in anthrax-infected guinea-pigs—was not successful; nor were most of those experiments made subsequently in various protozoal and bacterial infections, including tuberculosis, by himself, Behring, Ehrlich, and other contemporary workers, using the older antiseptics and the newer synthetic dyes (methylene blue, however, was shown by Ehrlich and Guttman in 1891 to have some value in malarial infection). Indeed, by 1900 the number of chemical remedies that could be said on scientific evidence to deal directly with the causes of infective diseases had scarcely increased, and Dale (1943) describes this point as about the low-water mark of interest and confidence in the remedial value of drugs. The hope of bringing specific chemical substances into therapeutics, which the discovery of the aetiological role of micro-organisms

had aroused, gave way to hopes based on specific immunotherapy, which had already produced such signal successes.

Yet, a few years later, the general outlook changed when the first great advance was made in the use of synthetic substances in chemotherapy; for in 1904 Ehrlich and Shiga produced virtually the first modern chemotherapeutic achievement—the rapid sterilization of an experimental trypanosomal infection (*T. equinum*) with a chemical synthesized for that particular purpose (trypan red). This was followed by further successes in the field of trypanosomal and spirochaetal infection, culminating in the first unequivocal application to human therapy—the use of salvarsan in syphilis in 1910 by Ehrlich and Hata. These successes were largely due to the systematic search by Ehrlich and his colleagues among synthetic coal-tar dyes and organic arsenicals in conjunction with test-tube and animal-infection tests. Here was the exploitation of the relation of the activity of therapeutic agents to their chemical structure, the “biological experimentation carefully co-ordinated with constructive chemical manipulation” (Lewis, 1917a) that is the very essence of therapy with synthetic chemicals. In contrast to these successes among the protozoa, *in vivo* laboratory experiments with synthetic substances in systemic bacterial infections during this decade were still negative or inconclusive, even though the substances used might be strongly inhibitory to bacterial growth *in vitro*.

A few years before Ehrlich and Shiga's historic success with a synthetic substance there was also a small but significant advance in the use of agents of microbial origin in chemotherapy when in 1889 Emmerich and Löw published their experiments on “pyocyanase” from *Ps. aeruginosa*. This work had been preceded, as Florey's (1945) fascinating review shows, by 20 years of scattered observations on the antagonistic relations of micro-organisms, following Pasteur and Joubert's original report, and including attempts to cure or protect animals infected with one species by administration of an antagonist. In these earlier *in vivo* experiments the antagonist had been provided mainly by whole bacterial cultures (living or sterilized), and, indeed, Cantani (1885), of Naples, claimed some success in human pulmonary tuberculosis by the insufflation of a particular saprophytic bacterial culture designated as “*Bact. termo*.” Now, however, apparently for the first time, a bacterial extract was found efficacious in experimental infection, for Emmerich and Löw reported that the injection of pyocyanase preparations could protect rabbits against anthrax; and cures of animals after infection were also noted with similar preparations. In the first decade of the century pyocyanase came into widespread clinical use in various infections, at first internally and later mainly by local application, but in spite of promising early results its use was eventually more or less abandoned, possibly with insufficient reason. During this period little further success was evidenced in microbial therapy in general, in either experimental or human infections; and I can find no record of the inhibition of growth of tubercle bacilli by the actual products of micro-organisms, even *in vitro*, before 1912.

Reversion to General Measures

What was happening during these 30 years in the field of human tuberculosis? The modern conception of immunity in this infection originated from Koch's experiments from 1891 onwards, and was added to by the results of necropsy series (Kuss, Naegeli, etc.) and of the diagnostic tuberculin test (Koch, Pirquet, Mantoux, etc.) in man; while the concrete turn given to the idea of contagiousness by knowledge of the transmission of the infecting micro-organism canalized preventive action into hygienic measures, sputum disinfection, etc. As regards treatment, after the initial high hopes of specific cure of tuberculosis by chemical agents which were raised by Koch's discovery of the bacillus, the change of emphasis from chemotherapy to immunotherapy (to which we have already drawn attention generally) became particularly evident, since Koch's production of old tuberculin in 1890, and his experiments on guinea-pigs with this and later similar products, caused his attention to be focused on tuberculin as a remedy in man; and in so doing he may have actually impeded therapeutic progress. Thus, Koch prefaced his description of tuberculin by naming a number of drugs (mercury salts, gold cyanide, etc.) that he

had found tuberculostatic in the test-tube but ineffective in animals; whereas he had found that tuberculin specifically and effectively acted on tuberculous tissue and in that way rendered the pathogenic bacteria harmless without injuring the body. Small wonder if the aim of chemotherapy, as applied to tuberculosis, received a setback and tuberculin therapy became the vogue. But when, after a tremendous wave of enthusiasm, confidence in specific treatment with the various tuberculins also began to wane in many quarters, and still no chemotherapeutic agent appeared to stand the test of controlled scientific experiment, many of the more critical physicians fell back on general measures to strengthen the patient's resistance—fresh air, rest, diet, etc. The still few but increasing number of sanatoria and special hospitals assisted in these measures, though ultimate results were so often disappointing. It may be recalled also that the first dispensary was opened by Robert Philip in 1887, and that in 1894, following isolated preliminary observations during the previous 70 years, Forlanini published his first series of results of artificial pneumothorax, though the latter treatment was not to become general for another 20 to 30 years.

Certain anti-phthisical drugs of the period, nevertheless, had a reputation for exerting either a specific direct action on the infecting organisms or an indirect effect through stimulation of host defences. These were substantially the same empirical and traditional remedies that we have listed as in use before the discovery of Koch's bacillus, though new reasons, often of tenuous nature, were offered for their supposed effects: salts of inorganic arsenic (and the recently introduced organic cacodylate), which not uncommonly resulted in liver damage; tannin, despite the fact that no inhibition was found in contemporary guinea-pig experiments; creosote and its derivatives, sometimes in enormous dosage, on the dubious rationale that a protective tissue reaction was promoted around the tubercle; cod-liver oil; iodides; and a revival of calcium administration (popular in antiquity, recommended in the 10th century by the Persian physician Mowaffak, in the form of powdered crayfish), on the assumption that it counteracted a supposed demineralization accompanying tuberculosis (see Piéry and Roshem, 1931). In addition to these standard remedies, salts of copper (A. and E. Luton in France) and gold (White (1891) and Gibbes and Shurly (1892) in the U.S.A.) were used sporadically; while a few clinicians attempted straightforward internal disinfection of their patients with antiseptics, despite lack of evidence of efficacy in non-toxic doses in animals. Thus, Dr. Vere Pearson recalls (1946) that Dr. Robert Maguire, a physician to St. Mary's and Brompton Hospitals around the turn of the century, gave a weak solution of formaldehyde intravenously, and that this, as well as a weak silver salt, had a vogue for a few years. I have omitted mention of the innumerable “consumption cures” of this period, whose patent lack of scientific basis did not get them far; and we are not concerned with symptomatic medication, for which, of course, a considerable number of drugs (including creosote) were used for apparently sound reasons.

1910–1935

So far, even taking into account the very suggestive experiments with pyocyanase, there had been no unequivocal demonstration of the chemotherapeutic sterilization of a general infection of bacterial origin in the animal living body. The cure of pneumococcal septicaemia in mice by Morgenroth and Levy in 1911, using “optochin,” a synthetic homologue of quinine, raised hopes in this direction, even though this experiment proved inapplicable to human therapy. But while, during the next 25 years, important new local antiseptics came to the fore in the control of bacterial wound infection and infected mucous membranes, particularly as a result of the first world war, attempts to effect cure of a systemic bacterial infection in man by internal chemotherapy were persistent failures. With the possible partial exceptions of new chaulmoogra derivatives in leprosy, and of sanocrysin and related compounds in tuberculosis (see later), mycobacterial infection shared in this failure. Ehrlich's (1914) warning, given at the International Medical Congress in London two years before his death, of the hard struggle that would be required for success in antibacterial chemotherapy—above all in tuberculosis—proved only too correct. Even local disinfection in tuberculosis was fraught with difficulty—witness the inconclusive

results with certain essential oils, such as "gommenol," in the pleural cavity.

Of the many chemicals—both new ones, and old ones in new forms—that were tested in the laboratory for anti-tuberculous activity during this period, some of the more important will be briefly discussed (for fuller surveys see Cummins, 1930; Wells and Long, 1932; Findlay, 1940).

Dyes—Cod-liver Oil—Chaulmoogra Oil

Various aniline dyes and chemical modifications thereof were investigated by Paul Lewis (1912-17), De Witt (1913-23), and others. Some—e.g., azo-dyes, members of the acridine series, and other basic dyes—showed selective inhibition of growth of the bacillus in the test-tube as compared with other bacterial species. Some, either alone or in a chemical combination with other agents such as metals, phenol, or iodine, penetrated and inhibited the bacilli *in vitro* and were able to penetrate the tubercles in the body; but while they might extend the life of infected guinea-pigs and rabbits and reduce the anatomical extent of the lesions—one of the most encouraging in this respect being methylene blue and its derivatives—they did not prevent or cure the experimental disease. None of these dyes found a place in internal medication in man.

Another group tested experimentally was creosote and many allied preparations (e.g., thymol)—popular empirical remedies, as already stated. They were not found to be very highly bacteriostatic *in vitro*, and animal infection experiments failed to give evidence definite enough to justify their clinical use in tuberculosis on grounds of specific antibacterial action—any good results were more likely to be due to non-specific symptomatic effects.

Much experimental work was done during this period to find a rationale for the traditional use of cod-liver oil in human tuberculosis. On analogy with the apparent value of fatty acid fractions of chaulmoogra oil in leprosy, sodium morrhuate was investigated in the laboratory and was applied clinically in pulmonary tuberculosis, in lupus vulgaris, and in sarcoidosis, but the results were inconstant (Cummins, 1925). Despite this, the presumed benefit of cod-liver oil was—and still is—asccribed by some to a direct antibacterial action of component fatty acids. After the discovery of the fat-soluble vitamins, another hypothesis for the clinical benefit of cod-liver oil arose—namely, its A or D content. The few experiments on the effect of vitamin A deficiency in experimental tuberculosis were inconclusive (Steiner, Greene, and Kramer, 1937b), but the more commonly held possible explanation was the mobilizing action of vitamin D on calcium. In spite of the apparent association of calcification with healing, there was little clear direct experimental evidence in support of either calcium or vitamin D therapy (Mayer and Wells, 1923; Grant *et al.*, 1927, 1930; Steenken and Baldwin, 1937; Steiner, Greene, and Kramer, 1937a); nevertheless, the value of these substances has been persistently maintained by many clinicians, and one hesitates to deny that the importance of calcium or phosphorus metabolism in tuberculosis treatment may yet be revealed—certainly the vitamin D factor in cod-liver oil requires re-examination in view of the recent clinical reports by Charpy and Dowling of regression of lupus after giving calciferol.

The possibilities in tuberculosis of the leprocidal chaulmoogra oil itself, and of its cyclic unsaturated fatty acid constituents—e.g., chaulmoogric and hydnocarpic acids (which had been isolated a little before the beginning of this period)—were also investigated; and structurally similar many-carboned fatty acids, containing rings or branched chains, were synthesized (see Robinson, 1940). Many of these natural and synthetic substances were tuberculostatic in the test-tube (Walker and Sweeney, 1920; Stanley *et al.*, 1932). A number of them were tested in experimentally infected animals, and some prolongation of life and suppression of lesions claimed, but the matter remained in doubt; trials in human pulmonary tuberculosis also were inconclusive (see Wells and Long, 1932; Emmart, 1946). As will be noted later, interest in chaulmoogra derivatives and allied synthetic compounds, as well as in long-chained fatty acids in general, has been recently revived, and with more promise.

It is not possible to enumerate more than a few of the many other chemical substances that were investigated or reinvestigated *in vitro* or in experimental animal-infection during these 25 years. They include cinnamates, terpenes from essential oils (Courmont), and a variety of other organic compounds (e.g., see Kuroya, 1929; Meissner and Hesse, 1931; Hesse and Meissner, 1931); iodine and iodides; minerals such as coal (Cummins and Weatherall, 1931); and compounds of metals such as arsenic, mercury (De Witt, 1921), copper (Linden, 1912, 1920), and, above all, gold (Feldt, De Witt, Möllgaard), both in organic and in inorganic forms. The *in vitro* activity of some of these substances was high, but either they were toxic or the results in infection experiments proved mostly negative or indecisive. Where they were apparently positive, as with some compounds of the heavy metals, the benefit was ascribable usually to an indirect effect of local tissue reaction or of stimulation of

immunological or other defence mechanisms. The particular approach of Walbum (1921-9; Walbum and Boas, 1931) may be mentioned; the use of minute doses of a number of metals under certain conditions, especially cadmium and manganese, was stated to affect the immunological reactions of the body towards the infecting tubercle bacilli.

Early Work with Antibiotics

In comparison with the many chemotherapeutic attempts against tuberculosis, using the above-mentioned natural and synthetic compounds, reports of results obtained with antibiotic substances of microbial origin during these 25 years were very few; and, reading the literature, one is struck by the lack of connexion between these two streams of scientific endeavour.

Rappin (1912), having found that filtered broth cultures of certain spore-forming bacteria—*B. subtilis*, *B. mesentericus*, and *B. megatherium*—were active *in vitro* against *M. tuberculosis*, injected tubercle-infected guinea-pigs with culture filtrates from *B. mesentericus*, and reported that the disease was thereby prevented or suppressed and that no toxic manifestations followed the injections. About the same time another Frenchman, Vaudremer (1912-13), described a substance obtained from *Aspergillus fumigatus*, in contact with which tuberculin was inactivated and tubercle bacilli lost their pathogenicity for guinea-pigs and rabbits. Although Vaudremer apparently made no direct protection experiments on infected animals, he reported that clinical trials of his extract were in progress in cases of pulmonary tuberculosis in Paris hospitals; the extract was well tolerated, but preliminary results on 200 patients were inconclusive. These, probably the first chemotherapeutic experiments with antibiotics in tuberculosis, are particularly interesting in the light of present intensive laboratory study of the potentialities, both of the genus *Aspergillus* and of the *B. subtilis* group of spore-formers, against this mycobacterium. Little further progress seems to have been made as an immediate result of the observations of Rappin and Vaudremer, and in most of the publications during the next 25 years on antagonisms against tubercle bacilli the antagonist was in the form of whole cultures and not the latter's separated antibiotic products. These reports provide evidence of lysis, death, or loss of virulence of tubercle bacilli produced by cultural association with, or by addition of, the antagonistic micro-organism: the latter included *B. subtilis* (Van Canneyt, 1926; Schiller, 1930); *B. mycoides* (Much and Sartorius, 1924; Kimmestiel, 1924); "*B. tuberculophilus*" (Puntoni and Favia, 1934); an anaerobic bacillus (Passini, 1926); *Escherichia coli* (Peretz, Newler, and Larionow, 1936); a staphylococcus designated *M. antibioticus* (Dujardin-Beaumetz, 1932, 1934); and yeasts (Schiller, 1925, 1927). It may be noted that culture filtrates from Much's cytolytic bacillary strains were active as well as whole cultures, and that a lysate of tubercle bacilli was used in human therapy; while in Schiller's experiments with yeasts and *B. subtilis* the organism to be attacked apparently played a part in "forcing" the antagonism: but neither of these authors produced clear evidence of inhibition of the tuberculous process in the body through an antibiotic effect.

While the tremendous amount of information accumulated by all this anti-tuberculosis chemotherapeutic research has been and will be of considerable value, and some of the synthetic and natural substances are being submitted to further study and development, the sum total of short-term practical gains to the clinician must, in retrospect, be regarded as meagre. A number of the drugs investigated in the laboratory found their way into contemporary therapeutics, often without full justification, but their favour was mostly short-lived or local; and the same applies to Vaudremer's antibiotic. The outstanding exception was gold therapy.

The "Gold Decade"

The years 1925-35 might be termed the "sanocrysin" or "gold" decade in tuberculosis treatment. The more recent background to that period was as follows. Koch in 1890 reported that simple gold salts were strongly inhibitory to the growth of tubercle bacilli *in vitro*, but ineffective in experimental tuberculosis in guinea-pigs. Nevertheless, success was claimed with gold salts in phthisis by some clinicians of that time (see above). Spiess and Feldt in Germany during the 1914-18 war recommended a gold-canthalidin compound, followed (Feldt, 1917) by an aromatic compound of gold called "krysolgan," which was used principally in German clinics but had lost much of its popularity by the time "sanocrysin" became general. While highly active *in vitro*, this compound's introduction into clinical practice had a rather insecure foundation in animal experiments. Meantime De Witt, in the

U.S.A., investigated various gold compounds in experimental tuberculosis, with negative results, so that gold therapy did not look promising (De Witt *et al.*, 1916, 1918; De Witt, 1918). Then, in 1924, Möllgaard introduced a preparation of sodium aurothiosulphate as "sanocrysin," believing this to be the answer in Ehrlich's sense—i.e., a substance that would reach and attack the bacilli, active *in vitro*, and able to prevent the experimental disease in animals without serious damage to the host's tissues. Rarely, wrote Secher (1927), who first applied the drug clinically, had a therapy been so well based on experimental work. Subsequent events threw doubt on this assertion, for while some eminent workers (e.g., Madsen and Mörch, 1926-7) confirmed and extended Möllgaard's striking claims in experimental tuberculosis, others reported in an opposite sense, and Okell and Parish (1931) concluded that "tuberculosis in guinea-pigs is not influenced by sodium aurothiosulphate." Again, the *in vitro* inhibitory action of sanocrysin was found to be markedly affected by body constituents, etc., and the view gained ground that its action *in vivo* was not directly bactericidal but was indirect, through stimulation of tissue cells, possibly of the reticulo-endothelial system, or through excitation of hyperaemia in the tissues round the tuberculous foci, rather as tuberculin and other salts of gold and various heavy metals were presumed to act (see Cummins, 1930; Wells and Long, 1932).

Sanocrysin was given to the medical world in 1924 as a specific, and most of the profession accepted it, partly perhaps as a welcome change from tuberculin. Möllgaard's preparation was followed by others from various sources, some of which could be given intramuscularly instead of in the vein. A mass of papers was published (those up to 1933 are reviewed by Cummins, 1933). Gold caught the public imagination, as is evidenced by the popularity of the rhymes technical and not so technical that were written around it.

After a period of rather indiscriminate application with high dosage, a more cautious attitude gained ground; and more mature views as to the best indications for gold therapy in pulmonary tuberculosis may be expressed as follows (there being some overlap): (1) in recent "exudative" lesions; (2)—perhaps the best indication) to check exacerbation—e.g., in subacute or chronic disease with fresh spread, or in contralateral extension occurring in the course of pneumothorax treatment; (3) to check constitutional disturbance. Gold was, however, persistently used in a variety of cases, in some of which it could, at the best, provide only a placebo.

Although the fatalities of the earlier years were reduced by general acceptance of smaller dosage, objectionable and sometimes dangerous acute or subacute complications were increasingly and persistently reported. The recognition of toxicity, and the inconclusive nature of the benefit conferred, were the main factors in the decline in the use of gold in tuberculosis.

A rough measure of the waxing and waning of interest in this therapy is given in Fig. 1, which shows, from 1925 (when sanocrysin

Fig. 1.—Graph showing the number of papers on gold treatment in tuberculosis listed in the *Index Medicus* during the years 1925 to 1944.

was first in general use) to 1944, the total annual number of papers referred to in the *Index Medicus* under the heading "Gold Therapy in Tuberculosis," and the number of papers dealing primarily with toxic effects. The graph shows a first wave of publications, then a decline, then a second wave reaching its peak in 1934-5, after which

there is a steady decline up to 1939 and after. It will be seen further that, after a virtual absence during the first six years of papers reporting primarily on toxic effects, their number rises and remains a substantial proportion of the total. The low level of the curve of publications at its end-point is a reflection of the fact that at the present time gold is seldom used for the commoner forms of tuberculosis, except by a few stalwarts: thus, inquiry at three large county tuberculosis institutions in the London area elicited that in 1944 the percentages of patients discharged in whom gold therapy was used were 3.1 (Clare Hall), 0.9 (Harefield), and 0.7 (Colindale), as compared with corresponding percentages in 1938, in the first two hospitals, of 17.8 and 5.7.

This astonishing acceptance of a remedy, and its subsequent rejection without any immediate better substitute, is only equalled by the preceding, but overlapping, dramatic rise and fall of tuberculin therapy. I have considered this phase at some length because the several probable explanations serve also as a lesson for future chemotherapeutic assessments.

(1) The laboratory groundwork on the curative effect of sanocrysin was insecure, and the drug was heavily sponsored for general therapeutic use without adequately critical clinical trials. (2) The drug's toxicity relative to presumed effective dose was at first underrated. (3) The clinical benefit was not dramatic or constant enough to dispense with balanced controls, which were in fact rarely used, and where they were (Amberson *et al.*, 1931) the results were discouraging. (4) Investigation was rendered difficult because, as Cummins (1933) points out, pneumothorax treatment (which was extending rapidly contemporaneously) was naturally given preference, with the result that sanocrysin tended to be elbowed out and to be used on the less favourable forms of the disease, in which assessment of effect is equivocal; this is less likely to happen now, when the more discriminating use of collapse therapy leaves opportunity for many early cases to be submitted to controlled chemotherapeutic test.

Opinion is still divided on the real value of gold therapy in pulmonary tuberculosis. A few—e.g., Cohen (1943)—hold that, prudently administered on judiciously selected cases, it still has a place; but the undoubted majority consider that, although, like tuberculin, it may produce some advantageous effect in certain types of lesion, the danger makes the risk hardly worth taking.

To bring the use of heavy metals up to date, I should add that (in addition to Walbum's special application) cadmium has been advocated as a less toxic substitute for gold, but without finding much general favour (see Heaf, 1937; Cornwall, 1938; Schedtler and Rodiger, 1941).

The End of the Period

The end of this section of our survey—1935—saw a general and probably healthy reaction among clinicians against drugs in tuberculosis, apart from a few valued symptomatics. The lack of a scientific basis for most of the traditional empirical "specifics" mentioned earlier had won more or less general acceptance among the medical profession, with their consequent virtual disappearance from therapeutics. Two important exceptions were cod-liver oil, still enjoying world-wide repute, and calcium preparations (e.g., calcium gluconate), strongly advocated in some Continental countries. Replacements of the traditional remedies by newer drugs reported on favourably from the laboratory, sometimes on inconclusive evidence, had been limited and temporary. The crest of the wave of interest in gold therapy had been passed. If we add to this negative list the fact that tuberculin as a means of treatment had been generally abandoned except for certain eye, genito-urinary, and other special conditions, a diminution in faith in the specific approach—immunological or chemotherapeutic—to the treatment of tuberculosis is hardly surprising. "No treatment at present can be aimed directly against the causal agent . . ." concludes Browning (1935) in a lecture on chemotherapy; "immunization does not appear to influence the established disease, and the only procedures commonly approved consist in conserving general health, resting affected parts, and removing necrotic tissue"; but he adds that "it is difficult to believe that we must remain bankrupt in methods of directly attacking the tubercle bacillus."

Positive advances in other fields of anti-tuberculosis activity during the preceding 25 years provided compensation for the

setback in specific treatment. Sanatoria had expanded in number and developed in scope, both for pulmonary and for non-pulmonary cases. In Britain the National Tuberculosis Scheme, inaugurated in 1912, had proved its worth. Artificial pneumothorax and other forms of collapse therapy had come into their own, particularly from 1920 onwards, when radiographic control became reasonably practicable. Much greater emphasis was being laid upon preventing the disease by reduction of contagion and by insistence on contact examinations. The understanding of the immunology and epidemiology of tuberculous infection had been advanced by the work of Ghon, Opie, Cummins, and many others.

[Part II, with a full list of references, will appear in our next issue.]

WEIL'S DISEASE: A RARE CONDITION ?

BY

KENNETH ROBERTSON, M.D., M.R.C.P.

Honorary Physician, Royal Hants County Hospital, Winchester,
and Royal South Hants Hospital, Southampton

An attempt is here made to establish a number of conclusions relating to this disease, which is still generally regarded as of academic interest only. In the first place, we are convinced that the infection is not by any means a rare one, nor is it likely to be encountered only by those whose work brings them into contact with certain industrial groups, such as sewer workers and miners. Secondly, we believe that it is not unreasonable to expect a diagnosis to be made within the first few days of the illness upon clinical methods alone, and that the only requirements are a familiarity with the characteristic picture as seen at this stage of the disease and a knowledge of a number of special points to be looked for and of simple laboratory investigations which must be carried out. Thirdly, as a result of our early recognition of suspected cases we have had the opportunity of watching the effect of specific treatment given at this stage of the infection, and our observations have left a feeling of confidence that this is of real value and may even be life-saving. Finally, as a result of considerable familiarity with the condition, a number of observations have been made which we believe have not been recorded before. We feel that a note on these may be of value.

Frequency of the Disease

In July, 1936, when Weil's disease was to us nothing more than an almost forgotten name, a case came under our care which proved to be a very typical example of this illness. A year later a second case was recognized, and by June, 1938, we had dealt with four such cases. These four cases were of particular local interest, for it appeared that in each case infection had been the result of bathing or working in the same stream (Robertson, 1938). During the next seven years a further 30 cases have been seen—that is to say, we have been encountering the condition four or five times every year.

So far as we have been able to ascertain, the total number of cases recognized during this time in the area in which our work is carried out has certainly not exceeded 40. These rather remarkable figures can surely indicate only two things: the relative frequency of the infection, and the ease with which it has been able to evade recognition.

Recognition

Excellent accounts of the clinical picture are available in textbooks and have been elaborated by numerous workers elsewhere, so that only a brief reference to this is needed here. The infecting organism, *Leptospira icterohaemorrhagiae*, is carried by the rat, and it can be assumed that something like 40% of all rats are infected. The leptospira leaves its host by way of the animal's renal tract. Human infection occurs as the result of contact with water which has been contaminated by rats' urine. Only fresh water can become infective, as quite small amounts of salt render the organism inactive; while direct sunlight has a similar tendency. Stagnant water is more dangerous than that of a freely flowing stream.

Under these conditions the leptospira can probably survive indefinitely. The incubation period appears to be about ten days.

No age is immune, and we have seen the disease at all ages from 5 to 78 years. Characteristically, the onset is abrupt and the victim has been in good health. The symptoms are high fever, often a rigor, severe headache, generalized pains, not infrequently gastro-intestinal symptoms, haemorrhages from some part of the body, and in about half the cases jaundice of varying degree after the fourth or fifth day. In some of the more severe and jaundiced cases serious renal impairment appears, with an increasing retention of nitrogen, sometimes terminating in anuria. It is in this group of cases that fatalities occur.

It must be emphasized that half the cases, whether treated early or not, show no jaundice at any stage of the illness, and among these the incidence of a lymphocytic leptomeningitis is very high. Probably all cases show a peculiar conjunctival suffusion at some time, though this may be transient and may be missed.

Of particular significance are the muscle pains. These are often intense and may persist for several days. The pains are in muscle and are not related to the joints. During this phase pressure over muscle, particularly in the limbs, is often intolerable, and this objective finding almost always persists for several days after the subjective symptoms have subsided.

The headache is severe and by its occipital predilection suggests meningeal involvement; this is often further emphasized by the presence of neck rigidity and a positive Kernig's sign. These findings usually make lumbar puncture inevitable; indeed, several of our cases reached us with the diagnosis of meningitis already made. The cerebrospinal fluid is frequently under pressure and is always water-clear. Pathological examination even in a case with very pronounced meningism may be quite normal when the routine tests are applied; but more often there is slight increase in protein, with a pleocytosis which may reach several hundred cells per cubic millimetre. The sodium chloride level is always normal. If the urea content of the fluid is investigated it is found invariably to be raised above the level which would be regarded as normal for the patient's age. In the laboratory which carries out most of our work the urea content is determined in all lymphocytic fluids which show a normal amount of chloride. This simple arrangement has been of great help in detecting a few early cases.

Haemorrhages are seen at some stage of the illness in most cases, and these may appear early. They may be from the nose, the gums, the gastro-intestinal tract, or into the skin and mucous membranes. When herpes labialis is present it is often haemorrhagic. In some cases a curious mottled appearance of the palate is seen; this was first pointed out to us by Dr. Evan Jones, and has been seen four times. It has not been possible by haematological investigation to determine the cause of this tendency to bleed. Bleeding times, clotting times, and platelet counts have always been normal; the prothrombin level has not been estimated in our cases.

The urine usually shows the presence of albumin, often cylindruria is observed, and not infrequently red cells are present, but a normal urine does not exclude the diagnosis. Often the white cell count is unaltered in the first few days. This statement is the reverse of what has usually been recorded, but time and again we have noted this normality. When jaundice has appeared the rule is a polynuclear leucocytosis, thus helping to differentiate leptospiral jaundice from that due to infective hepatitis. By far the most important single pathological investigation is undoubtedly the determination of the blood urea level. In all our cases this has been raised from the earliest stages, and the level to which this has reached has always provided a useful indication of the severity of the infection.

It should be possible to detect the infecting organism in the blood stream during the first five or six days of the illness, either by direct examination of blood smears with dark-ground illumination methods, or by animal inoculation of the infected blood. We have been successful only once in this, and then by the latter method. It is our view that these diagnostic methods are unnecessary.