Thorax, 1980, **35**, 884–889

The gold rush 1925-35

R Y KEERS

From Port Erin, Isle of Man

ABSTRACT Although from the time of Koch onwards there had been desultory experiments with a variety of gold preparations in the management of pulmonary tuberculosis, gold as a recognised and accepted treatment did not emerge until 1925. In that year Holger Mollgaard of Copenhagen introduced sanocrysin, a double thiosulphate of gold and sodium, with which he had conducted an extensive series of animal experiments. The results of these were considered to justify its use in clinical practice and two physicians, Secher and Faber, undeterred by its toxicity, reported enthusiastically in its favour. Other Danish physicians followed but, alarmed by violent reactions, modified the dosage, an example followed by British workers. Encouraging results continued to be reported although each series contained a significant proportion of failures, and toxicity remained high. The first properly planned and fully controlled clinical trial took place in the United States and produced a report which was wholly adverse and which sounded the death knell of gold therapy throughout America. Until 1934-35 gold was used extensively in Europe but thereafter there was a sudden and largely universal cessation of interest and within a few years gold, introduced with such éclat and carrying so many high hopes, had vanished from the therapy of tuberculosis even though, at that point, no better alternative was available.

The gold treatment of tuberculosis vanished from practical therapeutics nearly 40 years ago but those interested in the history of this disease may still spend an intriguing hour pondering on the phenomenon of the gold decade, the years from 1925 to 1935 which witnessed both the steady rise of aurotherapy and the beginning of its sudden and precipitate decline.

Although the gold explosion did not really erupt until 1925 there had been antecedent rumblings dating back to the days of Koch. Until 1882 the weight of medical opinion, apart from that in one or two small but enlightened States in Southern Europe, had held firmly to the belief that phthisis was hereditary, a concept which did little to encourage optimism regarding the outcome of the disease in the individual case. Therapy was directed mainly towards the relief of symptoms and medicaments varied from simple galenicals and inorganic salts to bizarre and exotic compounds which were a measure of the despair and dread with which the disease was regarded. But Robert Koch's discovery of 1882, once its full significance had been appreciated (and the protagonists of the theory of heredity did not readily relinquish their cherished beliefs), opened up the pathway for therapeutic reappraisal and a new approach. There was now a direct cause to be assailed and the enemy—the newly discovered tubercle bacillus—would surely prove to be vulnerable to one or other of the powerful chemical agents which the physicians and the pharmacologists were eager to provide. Koch himself elected to lead the attack and conducted experiments with a variety of inorganic compounds among which was a double cyanide of gold and potassium. He referred to this work in an address to the International Congress of Medicine, meeting in Berlin in 1890, when according to Calmette, he claimed that "as little as one millionth part of the cyanide is enough to either prevent or arrest the development of the germ." Calmette also recorded that "G Rosenthal and, more recently, Stefan Pekanowitch attempted to profit by this fact and to treat patients with daily subcutaneous injections and even with intratracheal injections of five to 15 mg. This quantity was usually badly tolerated and had no good effect."[1] Koch soon forsook his chemotherapeutic researches and turned instead to immunotherapy, an unfortunate change of course which led him on to the tuberculin débâcle. But others, taking encouragement from the work of Ehrlich with arsenicals, carried on and in a short time J B White announced that he had obtained benefit both in animal experiments and in human patients by employing a double chloride of gold and sodium combined with iodide of manganese.[2] Interest in gold was now

thoroughly aroused and for a time numerous gold salts were recommended for tuberculosis but without any really convincing proof of efficacy. Thus Albert Calmette found that it was not difficult to accustom tubercle bacilli to growing in culture media in the presence of progressively increasing quantities of gold and "my collaborator, Maurice Breton had the same experience in using a solution of colloidal gold (0·125 g of gold per 100 cc) which M Fourneau of Paris was good enough to prepare for us. Guinea pigs injected with tuberculosis and later treated by subcutaneous injections of this colloidal gold died after the same intervals as the controls."[1]

Between 1912 and 1916 two German workers, Spiess and Feldt, devoted much time to the study of gold therapy and eventually emerged with a gold cyanide and cantharidin compound—monocantharidyl-ethylenediamine-aurous-cyanide—which they very understandably named Aurocanton and which they claimed had produced benefit in animal experiments. Unfortunately these benefits were not reproducible in clinical practice.[2] Meanwhile in the United States an indefatigable and highly esteemed research worker, Lydia De Witt, was investigating the use of various gold salts in experimental tuberculosis in guinea pigs. Both simple gold cyanide and the more complex compound of Spiess and Feldt were among those studied and "no or very little effect was seen on the disease, except that life in general was shorter and the disease more pronounced in the treated animals than in the controls."[2]

In the light of these discouraging results the prospects for a revival of interest in gold appeared dim and there was a hiatus of some years until a new figure appeared on the scene. With the arrival of Holger Mollgaard gold therapy really took off.

Just how Mollgaard became involved in experimental therapeutics is not quite clear. He had a medical qualification but practised neither clinical medicine nor pharmacology being Professor of Physiology at the Royal Veterinary and Agricultural College in Copenhagen. He appeared to be a great admirer of Ehrlich and his work and it seems possible that this admiration drove him to an attempt to emulate his hero. Be that as it may, he embarked on an extended series of experiments in the treatment of tuberculosis using a wide range of animals and an inorganic gold salt, a double thiosulphate of gold and sodium with the gold in trivalent form, which he named sanocrysin. Writing in April 1925 on *The Theoretical Basis of the Sanocrysin Treatment of Tuberculosis* he introduced his subject by stating that it represented "an attempt to build up a chemotherapy in the sense of Ehrlich and Morgenroth; it cannot be too strongly emphasised that this treatment is to be considered as a beginning only, and as probably showing a way out of the present embarras des richesses in the therapy of tuberculosis." To speak of an "embarras des richesses" in the circumstances of 1924–25 suggests a buoyant and optimistic outlook allied to a lack of knowledge of the state of the therapeutic art in regard to tuberculosis and of the attempts which had already been made by competent workers to find a solution to this problem. But Mollgaard pressed on. He had experimented with a variety of animals and had quickly discovered that his sanocrysin produced a multiplicity of reactions, some of which could be quite devastating. He divided these reactions into two groups and termed the first "sanocrysin shock" which he held to have distinguishing clinical features: "ordinarily it begins with albuminuria, which develops into a grave parenchymatous nephritis. Shortly after the appearance of the grave symptoms of nephritis (increasing albuminuria, cylindrical casts, and blood corpuscles in the urine) acute myocarditis appears. The third and last stage in the intoxication in animals affected with pulmonary tuberculosis is an extensive oedema of the lung which increases until the animals die, with frothy fluid exuding from the mouth and nose."[3]

This "sanocrysin shock" he ascribed to the release of toxins from tubercle bacilli killed by the action of the gold, and he claimed that it could be virtually eliminated by the administration of a serum which he prepared from animals previously injected with defatted, formalin-treated tubercle bacilli. By the use of this serum he claimed that the entire process of "shock", including the nephritis, could be reversed within a matter of hours. His second group of reactions were labelled "tuberculous reactions" and included "rise in temperature, exanthemata, loss in weight, faintness, and intestinal disturbances." These symptoms he regarded as differing from "sanocrysin shock" in that they appeared in animals either with a more chronic type of disease or which had been treated with his immunising serum. At no point did it appear to occur to him that straightforward metallic poisoning could well have been a prime aetiological factor in some, if not all, of these reactions. It is clear from the data provided in Mollgaard's early communications that treatment by sanocrysin was a high risk business and one in which the outcome would require to be unequivocably favourable to justify the hazards. He summarised his results as follows: "the combined sanocrysin-serum treatment has saved the life of even very gravely infected goats, calves, and monkeys and brought them into a condition of clinical healing. On the other hand, it appears evident from the experiments that a thorough sterilisation of the affected organs is very

difficult and probably very seldom secured in cases of grave infection. In four lighter cases and in one grave case I have been able to carry the cure through until the guinea pig test was negative. In all other experiments the guinea pig test has been positive." These results, with the persistence in so many instances of positive guinea pig findings, stopped well short of the complete success for which he had been hoping. They were, nevertheless, held to be sufficiently favourable to justify the use of sanocrysin in clinical practice, and two leading physicians stepped forward immediately to place themselves and their patients at his disposal—Dr Knud Secher, Physician-in-Chief of a Medical Department at Bispebjerg Hospital, Copenhagen, and Professor Knud Faber, Professor of Clinical Medicine in the University of Copenhagen.

Secher was first off the mark and quickly became enthusiastic though, as Kayne was to point out later,[4] the patients with pulmonary tuberculosis whom he encountered as a general physician were mainly observation cases who, after a brief stay, passed on to a sanatorium depriving him of the opportunity for detailed follow-up studies. It is to his credit that he did attempt a follow-up, publishing the results in 1931, when he summarised his views on sanocrysin thus: "I regard it as the best remedy we have at the present time, and believe that its use will mean recovery for many patients who would otherwise be without hope, and considerable curtailment of the illness for many more."[5] The figures with which he supported this laudation, however, call for comment. Out of a total of 365 patients he classified 221 as "well" though he fails to provide a precise definition of this term. It would seem to be of some relevance to note that of these "well" patients no fewer than 71 had been sputum negative from the outset while a further 86 suffered from pleurisy only. The remainder of the total of 365 were reported as showing "some improvement" in 80 instances while 64 were classified as either unchanged or worse. The inclusion among those who had done well of so many sputum negative cases and cases of pleurisy only was bound to impart an appreciable element of bias to his findings and conclusions, but he did not permit a small matter of statistics to quell his enthusiasm for the new medication. He believed in giving large doses of sanocrysin, starting with 0·5 g, followed by 0·75 g, followed by 1 g until a total of 7 to 8 g had been reached. He expected reactions to occur but discounted the risks involved: "I am convinced that better results are obtained by giving large doses which cause reactions than small doses which do not cause reactions."

Professor Faber, working in the University Clinic in Copenhagen, recorded his impressions of sanocrysin after he had been using it for approximately six months. He made it clear from the outset that he was prepared for serious reactions: "in the first few weeks we also had cases in which the reactions caused by the treatment could not be controlled, so that the patient succumbed before he otherwise would have done. We fairly quickly discovered, however, what the special dangers were . . . and in the last five months we have had no disasters of this kind."[6]

The incidence of reactions nevertheless remained high (many would have said unacceptably so), and among those commonly encountered Faber listed fever, general malaise with nausea and anorexia, vomiting, rash, and polyarthralgia, this latter being often quite severe. During the six months surveyed he treated 42 patients, patients in whom "the disease was so far advanced that an estimate of its effects could be formed" and in his report he claimed that "eight of these must be regarded as cured in that all subjective signs of the disease have vanished; the sputum, if still present, is always free from bacilli . . . and x-ray examinations show considerable changes . . . Most of these patients have left the hospital for several months and feel absolutely well. Another group of 17 patients has shown signs of very considerable improvement subjectively and objectively. Some of them are free from bacilli (eight), four others show only very few bacilli . . . A third group comprises nine where the treatment cannot be said to have done any positive good . . . Lastly, in six cases the disease has not been arrested by the treatment, but has rather tended to spread as time went on." In his concluding paragraph he expressed his belief that sanocrysin had a specific curative action on tuberculosis of the lungs, that it was very effective in fresh disease which had been present for less than one year, but that in older cases its effect was uncertain. Faber's report may be criticised quite legitimately on the grounds that he is claiming success after a totally inadequate period of follow-up, and he appears to have been unaware that much more than a few months of freedom from symptoms was essential before the claim of "cure" could justifiably be upheld.

Thus sanocrysin, an inorganic gold salt, the brain child of a physiologist who had developed an interest in experimental pharmacology, was launched upon a world which, craving desperately for a remedy for tuberculosis, was ready to clutch at straws. Controlled trials had not then become an essential feature of the therapeutic scene and, swept along by the encouraging reports from Secher and Faber, physicians in every country (with one notable exception as will be seen later) were prepared to

have a go. Initially most adopted the dosage scale recommended by the two Danes but the severe reactions associated with this high dosage led to a revolt: a reduction followed with a corresponding decline in the severity of the reactions though these were by no means completely abolished.

As more experience was acquired some of this early enthusiasm began to wane. Johannes Gravesen of Vejlefjord Sanatorium, a much respected and highly competent physician, reviewed a series of 270 patients whom he had treated with sanocrysin. Out of this total he selected for special retrospective study 26 cases showing fresh spreading disease without cavitation, and from his study of the whole series as well as this special group he reached the following conclusions: "in the light of our present knowledge the idea of finding a 'specific' to act equally on the different phases of pulmonary tuberculosis is Utopian and in this, sanocrysin, like so many other suggested methods of treatment has failed. Research at Vejlefjord Sanatorium has been specially carried out on a group of 26 cases with suitable clinical conditions. These 26 patients, all with acute phases of fresh spreading disease, responded well to sanocrysin . . . the conclusion is that sanocrysin, suitably administered, exerts a specific effect by 'cutting short' recent pulmonary disease. In the large majority of patients where early and late phases of the phthisis are intermingled, by combining sanocrysin and collapse treatment there have been results which could not be attained by either method alone . . . On pronounced 'tertiary' phases sanocrysin alone has no remarkable effect."[7] In his use of sanocrysin Gravesen opted for smaller doses than those of Secher and Faber and thus avoided the dire complications which they had reported but even so his series was not completely trouble-free, there being two fatalities which he regarded as being directly attributable to the drug.

An attempt at some sort of trial was made by Wurtzen and Sjorslev from the Tuberculosis Department of Oresunds Municipal Hospital in Copenhagen using 137 patients for whom sanocrysin treatment had been recommended. Of the 137, 84 accepted the advice and 53 rejected it; the latter made up the control group. As most of the patients had advanced disease the outcome contributed little to current knowledge other than a tentative conclusion that "sanocrysin was of considerable benefit as far as the immediate results of treatment are concerned.[8]" Sanocrysin treatment while originating in Denmark soon spread beyond the borders of that country. Norway and Sweden initially followed the Secher-Faber school in employing large doses but, horrified by the reactions, physicians recoiled from the affliction of such calamities on their patients for what was by no means an assured benefit, and according to Kayne, who visited the leading Norwegian and Swedish centres in the early 1930s, few of them pursued sanocrysin therapy even at a lower dosage. Hans Jacob Ustvedt, one of Norway's outstanding physicians, was later to summarise succinctly the Norwegian view of the place of gold in treatment. "The early idea that gold acts directly in destroying tubercle bacilli now appears to have been exploded. It is not an example of specific chemotherapy but a purely empirical treatment and the explanation of any effect that it may have is unknown. It must be emphasised that gold treatment is often accompanied by toxic effects . . . These are most marked after large doses, such as were used in the early days of sanocrysin treatment, but even small doses may produce undesired effects."[9]

In Britain sanocrysin was greeted with interest allied to a modicum of reserve. Most tuberculosis physicians were prepared to give it a trial but no single individual emerged as an out-and-out protagonist of gold therapy. Nevertheless a considerable volume of literature appeared, mainly accounts of groups of patients who had been treated, and two such reports by Mansell[10] and by Pask[11] have been selected as fairly typical examples. Mansell, reporting on 153 cases noted that "although the drug has been in clinical use for over seven years, there is yet no consensus of opinion as to its dosage, mode of action, and the type of case in which its use is indicated." Having reviewed his material he concluded that "clinical evidence is accumulating to show that, in cases of extensive exudative disease sanocrysin in small doses often has a beneficial effect which may at least be of economic value. There is as yet no convincing evidence that this effect is lasting." Pask's paper dealt with 36 patients, selected on the grounds that no improvement was taking place on sanatorium treatment alone. The group included cases of both exudative and fibrotic disease and no attempt was made to assess the two varieties separately. Eight patients failed to complete the course either because of the severity of the reactions or because the treatment "did not appear to be doing any good." On the basis of the 28 who did complete, Pask gave it as his opinion that sanocrysin appeared "to be the most useful adjunct to sanatorium treatment next to artificial pneumothorax," an opinion which, after studying the paper in its entirety, seems barely justified.

As reports spilled forth into the journals it seemed that the clouds of uncertainty which surrounded the whole subject of gold therapy were deepening. It became clear that nothing was really known of the mode of action of sanocrysin—or even whether

it acted at all other than to produce reactions. There were divergent views as to the type of case suitable for treatment, and opinions varied as to the optimum dose. Professor Lyle Cummins, tenant of the David Davies chair of Tuberculosis in the Welsh National School of Medicine, attempted to shed some light on this clouded scene in the course of a discussion at the Royal Society of Medicine in 1930[12]: "Sanocrysin at first unduly vaunted as a 'cure' or rashly condemned as poison is now gaining general acceptance as a useful adjunct in the treatment of tuberculosis. It was vaunted as a 'cure' because the apparently successful cases were not observed over a sufficient length of time. It was damned as a poison because it *is* a poison, just as surely as tuberculin is a poison, when used in large doses in severe cases of advanced tuberculosis and it was only when thus improperly used that it gave rise to lethal effects." Then, turning to the vexed subject of the type of disease likely to respond satisfactorily, Cummins affirmed that the pathological structure of the lesion was the governing factor but, realising that this offered little help to the worried clinician, he suggested certain clinical criteria: "when there is pyrexia even at rest, the unbalanced type of early focal disease may be presumed to exist and sanocrysin, if given at all, must be given with the greatest caution. When pyrexia is absent at rest but excited by exercise soon subsiding again on a return to rest . . . this type of case has proved, in my experience, to be particularly favourable for sanocrysin treatment, especially in young subjects. Where the patient is free from any rise of temperature even on hard exercise, it is useless to expect dramatic results from sanocrysin. Some results there may be; but I have found that such cases are better left to physiological treatment in sanatoria."

While physicians in Britain were using sanocrysin and trying to convince themselves that it did some good, arrangements were in train elsewhere for the one vital piece of research which had so far been lacking. Gold therapy had crossed the Atlantic where it was being viewed with scepticism and where the absence so far of a properly organised controlled clinical trial was seen as a major defect. In order to put the matter of its efficacy to the proof J Burns Amberson, later to achieve international fame as chief of the Chest Diseases Division of Bellevue Hospital but at that time consulting physician in tuberculosis to the Detroit Department of Health, undertook a clinical trial of the drug at the request of the Department, which provided the necessary funds. Although the number of patients involved in the Detroit trial was relatively small the trial was most meticulously planned and executed. In this regard it was far in advance of anything which had yet been attempted and consequently its conclusions were invested with an authority which had hitherto been lacking. These conclusions were as follows: "(1) This investigation proves the need and the merit of a carefully prearranged plan to be followed in a clinical test of a chemotherapeutic agent in tuberculosis patients. (2) We discovered no evidence in 12 cases, studied according to such a plan, that sanocrysin, given in small, gradually increasing doses up to a total of 6·1 g has a beneficial effect on pulmonary tuberculosis or its complications. (3) Compared with "control" cases more of our sanocrysin-treated cases became worse. The evidence is strongly suggestive that sanocrysin was at least partly responsible for the unfavourable trend of the disease in some of these cases. (4) Sanocrysin exerted definite harmful systemic effects in all our treated cases, partly as a secondary result of its action on the local tuberculous lesions, but mostly, we believe, by virtue of its own inherent toxicity. These effects were usually on the nutrition, gastrointestinal function, temperature, skin, mucous membranes, and kidneys. (5) One sanocrysin-treated patient died from parenchymatous degeneration of the liver and other effects which we interpret as gold poisoning. We could not anticipate this unfortunate outcome. (6) Because of the lack of definite evidence of benefit and because of positive evidence of harm which in some respects is long-term, especially in the kidneys, the use of sanocrysin, as we used it, is not justified."[13]

This report with its comprehensive detail virtually sounded the death knell of sanocrysin in the United States. One further attempt was made to assess its value when Arnold K Balls at the University of Pennsylvania was awarded a research grant for the purpose. The volume *Tuberculosis Medical Research*, published by the National Tuberculosis Association succinctly records the outcome: "the investigation was terminated at the end of one year; the results did not appear to warrant publication."[14]

In an attempt to diminish the toxicity of sanocrysin pharmaceutical manufacturers were working hard on the development of a less toxic gold salt. A number of new preparations were introduced, some for intravenous injection, others for intramuscular use, but none of these proved trouble-free and toxicity remained a significant problem.

By 1934 gold therapy had reached its zenith, a point well illustrated by D'Arcy Hart in his Mitchell Lecture of 1946 on the chemotherapy of tuberculosis.[15] In order to demonstrate the waxing and waning of interest in gold he included in his lecture a graph showing the number of papers on the subject which were listed in the *Index Medicus* during the years 1925 to 1944. A separate curve dealt with

papers concerned primarily with the toxic effects. The main curve showed two peaks. The first, occurring in 1927, represented the initial enthusiastic response to sanocrysin and was not paralleled by any significant number of reports on toxicity. After 1927 the main curve declined until 1930 when it began to rise again steeply reaching new and higher peaks in 1934-35. On this occasion there was a concomitant rise in reports of toxicity which, by 1934, made up a third of the total. After 1935 the pattern changed abruptly with a sudden and precipitate fall in publications, a fall which was maintained over succeeding years until by 1943, papers relating to gold therapy in tuberculosis had virtually vanished from the literature. Hart commented "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" and he lists four factors which he felt had contributed to the abandonment of gold as a "cure" for tuberculosis: "(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 under-rated. (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,[13] the results were discouraging. (4) Investigation was rendered difficult because as Cummins[12] 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."

Reading Hart's very carefully worded commentary on the sanocrysin story and noting the abrupt onset of disinterest in gold therapy with the precipitate and accelerating decline in related publications it is tempting to conclude that, somewhere about 1934-35, tuberculosis physicians suddenly came to their senses, realised that they had been putting their patients at risk in pursuit of a highly dubious benefit and collectively decided to call it a day. Nothing in the literature of the time suggests that the therapeutic armamentarium against tuberculosis was seriously depleted by this jettisoning of gold salts and no-one mourned their passing. Max Pinner in his authoritative textbook "Pulmonary Tuberculosis in the Adult" published in 1945 dismissed the whole sanocrysin story in a few lines: "most metals in some chemical combination or other have been studied. The latest one . . . is gold in the form of sanocrysin and a few other gold salts. Following most enthusiastic claims for its specific action, it followed many another "chemotherapeutic" agent to the stage of nonspecific stimulant and finally to oblivion."[16]

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