Speaking picturesquely, one notes various types of control over the vegetative functions—for example, the linking up of non-striated muscle with the nodal system and with the internal secretions so largely instrumental in carrying on gastro-intestinal functions. These controls are shown in the occurrence of intestinal peristalsis once or twice in each minute and intestinal contractions eighteen or twenty times in each minute, the latter movements serving as a motor pump to propel venous blood in the portal system to the liver. All of these forms of stimulation are linked with the sympathetic nervous system, and through the sympathetic ganglions with the central nervous system. Our knowledge of this interrelationship we owe to the fundamental work of Gaskell and Langley.

The work of Hunter and Royle has stimulated fresh surgical interest in the sympathetic nervous system. In this field Adson and his associates have been able to relieve megacolon, which so closely resembles the dilated oesophagus in cardiospasm, by removal of the lumbar sympathetic ganglions and their communicating branches. The operation effects its purpose probably by leaving the sacral sympathetic outflow, which is motor to the distal part of the colon, in sole control of this part of the bowel. Adson and his co-workers also have brought about marvellous relief in Raynaud's disease, in certain types of contraction of the blood vessels of the extremities leading to gangrene, and in certain types of arthritis, by removal of the appropriate sympathetic ganglions and their communicating branches.

SANOCRYSIN TREATMENT OF PULMONARY TUBERCULOSIS.*

BY

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SANOCRYSIN is an organic salt of gold, and was first used for the treatment of tuberculosis in man in 1923, after several series of experiments on animals by Professor Moellgaard. The exact action of sanocrysin on tubercle bacilli or tuberculous tissues is still a subject of controversy. It is now more than four years since this treatment was introduced into the British Isles, and it should be possible to form some estimate of its value. From the clinical point of view there are a number of questions which it is important to answer: (1) What are the dangers of sanocrysin treatment? (2) What is the correct dosage? (3) Has sanocrysin any value in the treatment of pulmonary tuberculosis? (4) What type of case is likely to benefit from the treatment?

In the following remarks an attempt will be made to answer these questions from the records of the 102 patients discharged from the Forster Green Hospital after sanocrysin treatment between 1925 and 1928. All these patients had tubercle bacilli in the sputum, and a high percentage of them were of the exudative type.

Professor Moellgaard's original experiments convinced him that sanocrysin was well tolerated by healthy mammals; rabbits, goats, calves, and monkeys were injected intravenously with 3 cg. per kilo of body weight without serious results. It had no injurious effects on the kidneys of healthy calves and rabbits in doses of 2 cg. per kilo of body weight, while larger doses in calves caused oedema of the epithelium of the tubuli contorti. Transient albuminuria (three to four days) sometimes followed the early injections, but by graduating the dose a tolerance could be produced. Symptoms, such as diarrhoea, loss of weight, and fever, did not appear after the injection of sanocrysin in healthy calves. The result of an injection of sanocrysin was quite different in a tuberculous calf. Often the animal died of shock in forty-eight hours, while severe albuminuria, haematuria, diarrhoea, and loss of weight occurred if the animal survived long enough for observation.

There has been much discussion on the interpretation of these reactions in tuberculous animals, which Professor Moellgaard attributed to auto-inoculation, resulting from the destruction of tubercle bacilli in the body by sanocrysin. He solved the difficulty of treating the calves by the use of a serum, and then produced some curative results in experimentally infected calves and also in naturally infected monkeys. So far as I know, the serum is not used now in conjunction with sanocrysin treatment in man. In proportion to body weight, the doses employed in these experiments were rather larger than any used now in the treatment of human tuberculosis; also the intervals between the doses were shorter. It is, however, most important to consider the body weight in each individual case, in order to avoid the danger of overdosage.

The elimination of sanocrysin is effected mainly through the kidney, and it has now been shown by McCluskey and Eichelberger that at least thirty days are required for all the gold to disappear from the urine. The same observers found that doses of 2 cg. per kilo of body weight had rather marked effects in normal dogs, causing vomiting, diarrhoea, and albuminuria. Studying mice, S. Kurosu found that the tolerance was raised by increasing the dose gradually. J. Frandsen found that sanocrysin was not injurious to the kidneys of normal rabbits.

To summarize our present knowledge of the toxicity of sanocrysin, it appears that the drug in a pure state is not injurious to healthy mammals in doses of 1 to 1.5 cg. per kilo of body weight. Tolerance is increased by graduated dosage, provided there is a sufficient interval between the doses. The kidneys are mainly responsible for its elimination, which takes place much more slowly than was first supposed. It is, moreover, much more liable to damage the tuberculous organism than the healthy one.

The question of dosage has occupied the attention of all who are employing sanocrysin. By decreasing the dosage too much one may fail to get positive results. On the other hand, the dosage which was originally employed in Denmark and the British Isles is undoubtedly excessive, and exposes the patient to grave risks. The original plan was to give half a gram and follow this by a gram two or three days later. If the patient survived these initial doses, one gram was given weekly five or six times. The great majority of deaths resulting from sanocrysin were associated with this high and intensive system of dosage.

On the other hand, many of the patients who were able to tolerate these high doses at short intervals made a remarkable improvement, and some have remained well for the past four years. Hyperpyrexia, intense focal reaction in the lungs, haematuria, albuminuria, anuria, and jaundice were among the symptoms which were liable to appear, usually after the second large dose of sanocrysin. In considering the question, it is important to remember two facts to which reference has already been made: (1) The complete elimination of sanocrysin from the body takes a long time. (2) By graduating the dose one is able to create a tolerance, and ultimately large doses may be injected without causing any severe symptoms. A system of graduated dosage has now been generally adopted, with lengthened intervals between doses.

In afebrile patients it is safe to begin with 0.25 gram, and to increase the dose by the same amount in arithmetical progression until 0.75 gram is reached, which dose may then be repeated four or five times. Usually this scale of dosage will be tolerated well by patients weighing from 8 to 10 st. With patients who are over 10 st. the final dose may be increased to 1 gram, and in very light or emaciated patients 0.5 gram should be regarded as a maximum dose. The interval between the early doses should be about a week, or longer if the symptoms of reaction have not subsided. The interval between the larger doses should be ten days, or even a fortnight. In the treatment of febrile patients one may begin with 0.05 or 0.1 gram, and increase the dose very slowly, if the injections appear to be doing good. Some patients are unable to tolerate sanocrysin, even in small doses, and in 16 per cent. of the cases in my series the treatment was abandoned when less than 2 grams of sanocrysin had been

* Read in opening a discussion in the Section of Tuberculosis at the Annual Meeting of the British Medical Association, Manchester, 1929.

administered. Five of these were very seriously ill, and treatment was stopped because of the progress of the disease, not on account of any reaction. The reasons for stopping treatment in the others were as follows:

Diarrhoea	...	...	...	...	...	7
Prolonged albuminuria	...	...	...	...	...	1
Focal reaction	...	...	...	...	...	1
Intercurrent tonsillitis	...	...	...	...	...	1
Fistula in ano...	...	...	...	...	...	1

Two of the patients underwent a full course of sanocrysin treatment subsequently, with satisfactory results.

There has been discussion as to whether it is advisable to give several courses of sanocrysin. No doubt others will deal with this point, but my experience of second or third courses is small. I have an impression that a second course should follow at a short interval, say a month or six weeks, and that if a second course is considered necessary exercise should be strictly limited between the two courses.

COMPLICATIONS.

Up to the end of 1928, 102 patients had been discharged from the Forster Green Hospital after sanocrysin treatment. Five patients were treated by the original method with large doses, and the remaining 97 patients were treated with graduated doses. By good fortune no serious accident occurred in the course of the treatment of the first 5 patients, but 3 of the 5 had diarrhoea, 3 had a scarlatiniform skin eruption, 4 had vomiting after the injections, and all of them showed a loss of weight during and after treatment, varying between $1\frac{1}{2}$ and $16\frac{1}{2}$ lb. In the 97 patients who were treated by graduated doses complications occurred less frequently. The following table illustrates the fact that complications have been less frequent in the later cases of the series.

	Cases 1-50.	Cases 51-102.	Total.
Marked febrile reaction	11	15	26
Slight febrile reaction	24	19	43
Prolonged febrile reaction	1	3	4
Albuminuria (transient)	15	11	26
Albuminuria (marked)	22	9	31
Vomiting	17	5	22
Diarrhoea	10	4	14
Loss of weight	21	15	35
Dermatitis	8	4	12
Neuritis	1	2	3
Stomatitis	13	2	15

There is little to add here to what has been written already about the complications. There was one case of persistent albuminuria, apparently due to permanent damage to the renal tissues. Stomatitis was noted in 15 patients, 13 of whom were males. Several of the cases were due to smoking, contrary to instructions.

The most serious complication which has arisen has been prolonged fever, with a spread of the disease in the lungs. This occurred four times in the series of 102 patients treated, and 3 of the patients died within a short time, the fourth making a good recovery after seven weeks of fever. This prolonged reaction has been noted also in 2 patients who are not included in this series, as they were still in hospital at the end of 1928. In the 2 latter cases the reaction has subsided, and there is now improvement. The 6 patients who showed these prolonged severe reactions were all "advanced" cases, according to the classification by signs and symptoms. They were all cavity cases, with considerable toxæmia, as shown by temperature and pulse rate. The reaction usually occurred towards the end of the course of injections, and in 4 of the cases it was probably due to a cumulative action of the sanocrysin. Of the other 2 cases, one, which recovered, developed a pleural effusion as a complication of artificial pneumo-

thorax treatment after the second injection. The other, also an artificial pneumothorax case, had a rupture of the lung and died four weeks later.

It is obvious that the dangers and troublesome complications of sanocrysin treatment are not to be ignored. It would not be justifiable to continue such a treatment unless there was a definite probability of obtaining substantially better results than by conservative methods.

BENEFICIAL EFFECTS.

Where sanocrysin is well tolerated there are beneficial results, which follow in a high proportion of the patients. In the majority of the cases tubercle bacilli have disappeared from the sputum. Often, but less constantly, there has been a rapid clearing up of the x-ray picture, heavy cottony shadows being replaced by well-defined markings, and by signs of contraction of the diseased areas in the lungs. When these changes are marked the absence of bacilli from the sputum is likely to persist, but when the x-ray picture shows little improvement tubercle bacilli will reappear in the sputum. The changes in the x-ray picture which follow sanocrysin treatment have been described minutely by several Continental physicians, and the phrase "sanocrysin lung" has been coined to describe the shrunken fibroid lung often observed at the conclusion of a course of sanocrysin. This contraction of the lung is most likely to occur in cases where the disease is lobar in distribution, and in other exudative types of disease resolution may take place without radiological evidence of much fibroid change.

The effect on fever which has not yielded to prolonged rest in bed is often very marked, and after a few injections the temperature may become normal. This improvement is followed later by a diminution of the pulse and respiration rates.

The physical signs often show a rapid improvement. On auscultation it is found that the areas of moist crepitations have cleared up, being replaced by diminished breath sounds. If the improvement continues, harsh breathing and prolonged expiration become marked, and crepitations are not to be heard, even after cough.

Besides objective signs of improvement, there is a striking change in the aspect of the patient when the treatment is successful. The phthisical facies disappears, and the flabby chest muscles become rounded and firm. Lastly, so far as it is possible to judge in the short period of four years, patients treated with sanocrysin have a lower mortality rate than untreated patients.

All tubercle bacilli positive cases discharged from Forster Green Hospital from July 1st, 1925, to December 31st, 1928, were traced in the spring of 1929. These patients were classified in three groups, according to the severity of the symptoms on admission. In the moderate group 80 per cent. of those treated with sanocrysin are alive, and only 63 per cent. of those who did not have sanocrysin treatment. In the advanced group, 58 per cent. of the sanocrysin-treated cases are alive, as compared with 30 per cent. of untreated cases.

RESULTS OF SANOCRYSYN TREATMENT.

In considering the results I have included all cases in which the treatment was attempted. Of these, 19 were very seriously ill when treatment was begun, and 13 of these are dead, although marked temporary improvement occurred in 8 of them. Of the 6 surviving patients in this group, 2 had a spontaneous pneumothorax, complicated by a mixed infection, and 2 had artificial pneumothorax.

An attempt has been made to analyse the results in the remaining 83 cases. First they were divided into three groups as shown in the following table.

	Alive.	Dead.
1. No evidence of cavity	21	3 = 12.5%
2. Radiological evidence only of cavity	29	6 = 17%
3. Clinical evidence of cavity	17	7 = 29%

The result was more remarkable when an attempt was made to classify the cases into "exudative" and "fibroid" groups, according to the x-ray picture.

	Exudative.		Fibroid.	
	Alive.	Dead.	Alive.	Dead.
No cavity	14	3	7	—
Cavity x-ray evidence only	18	5	11	1
Cavity clinically	7	7	10	—
Totals	39	15	28	1

There has thus been a heavy mortality in the exudative group, although many of them did well while under treatment. But I believe that the results in exudative cases could be improved on, if treatment were prolonged over a period of several months. Frequent x-ray examinations are necessary in such cases, and the patient should be kept at rest as long as any exudative foci can be seen on the x-ray film.

Possibly it may prove to be best to give several courses at short intervals. In any case, if active disease is present after sanocrysin treatment, artificial pneumothorax or phrenic avulsion should be considered, even if the temperature and pulse rate are normal. I think also that some exudative cases with cavitation should have a period of rest and tonic treatment before trying sanocrysin, which might be employed when the limit of improvement has been reached.

In the fibroid group, however, the results have been more satisfactory, as there has been only one death among 29 patients. It might be suspected that these patients would have done equally well without sanocrysin, but most of them had the treatment because they had failed to respond to routine measures. Of this group, 55 per cent. were discharged without tubercle bacilli in the sputum, as compared with 43 per cent. in the exudative group. Excluding 10 "cavity" cases, 72 per cent. of the fibroid cases were without tubercle bacilli on discharge.

Tuberculosis of the larynx was present in 8 cases of my series, and I do not think it contraindicates sanocrysin treatment, as the laryngeal condition usually improved, and 6 of the 8 cases are alive.

Cachexia, intestinal tuberculosis, and disease of the kidneys are contraindications.

It is often advantageous to combine sanocrysin and collapse therapy, especially in cases where there is widespread disease of one lung, with some active trouble in the better lung. If the case is acute, and the lung tissue is breaking down rapidly on one side, it will probably be necessary to collapse the worse lung immediately and try sanocrysin afterwards.

In another kind of case, when the patient has passed through the acute stage and shows some resistance, I have found it more satisfactory to give a long course of small doses of sanocrysin first, and to try artificial pneumothorax later.

When the disease is almost entirely unilateral, and collapse therapy is clearly indicated, I think sanocrysin should not be employed; later, if fresh foci of disease develop in the functioning lung, it may be of service. In my series 19 patients had artificial pneumothorax treatment, and satisfactory collapse was attained in 7, all of whom are alive at the time of writing. The collapse was only partial in 11 patients, and 5 of these are alive.

There are two types of pulmonary tubercle in which I think sanocrysin may be of value. One is the early exudative case in which the disease in the lungs is severe or widely spread, but in which there is some evidence of resistance. The other is the predominantly fibroid type of disease, when symptoms and tubercle in the sputum persist after several months of sanatorium treatment. In the exudative case I think it is important to begin sanocrysin treatment as soon as possible. In the fibroid

case sanocrysin should be withheld until sanatorium treatment has had a trial.

When there is disease of long duration, combined with an exudative x-ray picture, sanocrysin treatment is not free from danger, but in such cases it may be possible to combine it successfully with artificial pneumothorax.

In judging the results, it should be remembered that the type of pulmonary tuberculosis seen in hospital patients in Ireland is commonly severe.

I have been encouraged to persevere with sanocrysin treatment by the opinions expressed by my colleagues in Belfast and elsewhere. Certainly it is not a cure for tuberculosis of the lungs, but it is a valuable aid to treatment, if used with caution and discrimination.

ASBESTOS DUST AND THE CURIOUS BODIES FOUND IN PULMONARY ASBESTOSIS.*

BY

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ASBESTOS was woven into cloth before the time of Herodotus 450 B.C., but the history of the industrial disease pulmonary asbestosis dates only from A.D. 1900.

In 1899 a man was admitted to Charing Cross Hospital under the care of the late Dr. H. Montague Murray. The patient was suffering from pulmonary fibrosis of obscure origin. He had worked for ten years in an asbestos factory, and his occupation was suspected as being the cause of death, which occurred in 1900. The case was not published, but Dr. Murray, in his evidence before the Departmental Committee on Industrial Diseases in 1906, referred to the presence of spicules of asbestos in sections of the lungs.

The next case, and the first published, was recorded in 1924. The clinical history and histological appearances have been the subjects of papers in the *British Medical Journal* (1924-27), and in the *Journal of the Royal Microscopical Society* (1927). The findings upon which the diagnosis of pulmonary asbestosis was made in that case, and the results of further work on the curious bodies that have been found in the lungs in all necropsies in the disease are the subjects of this paper.

Asbestos and Asbestos Dust.

Asbestos belongs to the pyroxene or hornblende group of minerals, and is classed with syenite, granite, and porphyry. I scarcely need remind you that the igneous rocks were originally silicate solutions—compounds of silicic acid with earthy bases. Under certain physico-chemical conditions hornblende and serpentine pass into fibrous varieties and are then given the technical name "asbestos."

The infinite varieties of asbestos differ in their chemical constitution and physical characters, but I propose to deal with one type only—chrysotile—the average composition of which is:

Silica	40.87 per cent.
Magnesia	41.50 "
Ferrous oxide	2.81 "
Alumina	0.90 "
Water	13.55 "

The iron content may be important. It will be interesting to see whether the effects of the iron-free dusts of some Italian, Arizona, Finland, and Chinese asbestos are the same as in chrysotile workers.

Microscopically, chrysotile fibre consists of colourless refractile translucent strands, but intermingled with the fibre are masses of black angular particles, brown particles of all shades from light yellowish-brown to deep golden brown, and particles the colour of sapphire blue. The dust generated during the process of manufacture consists of fragments of fibre and translucent spicules split off from it.

* A paper read in a discussion in the Section of Occupational Diseases at the Annual Meeting of the British Medical Association, Manchester, 1929.