

THE TREATMENT OF TUBERCULOSIS WITH CYANOCUPROL.

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(Received for publication, February 7, 1916.)

The present paper deals with the clinical treatment of tuberculous patients with cyanocuprol. I believe it desirable to report the work as far as it has progressed, although the cases are still too few to permit conclusions regarding the efficacy of the preparation. A later communication covering this point may be expected.

General Considerations.

Koga¹ reported that the intravenous injection of cyanocuprol brings about a degree of reaction in tuberculous cases, which is proportional to the amount given in each instance. However, the relation between the reaction and the efficacy has not yet been definitely established. Too great a reaction produced severe effects on the patient and smaller doses have therefore been given. The reactions have thus been eliminated, but the results seem incidentally to have become inferior to those obtained by Koga with the larger doses. The tubercle bacilli in the sputum, also, did not show such a marked decrease as under the influence of larger doses.

Although cyanocuprol produces favorable results in the condition taken as a whole when administered in adequate doses, yet indifferent cases sometimes occur in which its efficacy is doubtful. This indifferent result may depend upon insufficient dosage. Moreover, the constitution of the patient and the nature of the pathological processes play an important part in determining the effects.

Indications and Contraindications.—Cases suitable for the application of cyanocuprol are far more numerous than for the tuberculin

¹ Koga, G., *J. Exp. Med.*, 1916, xxiv, 149.

treatment, since it may be administered in almost all instances of tuberculosis. Even in the final stages the preparation may be given without danger, although with little hope of improvement. Patients suffering from progressive tuberculosis in the third stage sometimes gave an unexpectedly good result, and high fever abated after an intravenous administration. Pulmonary hemorrhages sometimes occurred during the reaction period, but they were traced invariably to carelessness on the part of the patient. The data at hand suffice to state that the preparation does not influence injuriously pulmonary hemorrhages but rather increases the coagulability of the blood so that the hemorrhage may be arrested. Cases with fever in consequence of cold may be given the drug without inconvenience. However, it may be advisable to wait until recovery from the cold takes place before giving the drug. The drug may be given to tuberculous patients with chronic diseases of the heart and kidney, and glycosuria and beri-beri, but it must not be given to patients having irregular or accelerated pulse (*e.g.*, over 120) or weak tonus of the pulse. The preparation may be given during menstruation and pregnancy provided care be exercised to avoid any unusual reaction.

Dosage.—There exists an intimate relation between the proper dose and the condition of the patient, for upon the dose seems to depend largely whether or not improvement follows. We are now studying this point with the utmost care. It seems to be much more difficult to ascertain the proper dose of cyanocuprol for each individual than of tuberculin. For instance, in some cases a reaction set in in consequence of an increase of the dose by 0.25 cc., in others a rise of temperature occurred even when the same dose was given each time. The dose of tuberculin may be settled comparatively easily by the degree of von Pirquet reaction or the reaction produced by the intracutaneous injection of tuberculin. But with cyanocuprol we have as yet no preparatory test by which the dose can be determined. We are at present determining, according to our past experiences, the amount for each individual case by the following standard doses, which have been chosen with reference to the site and severity of the pathological processes.

TABLE I.

Type of disease.	Dose. cc.
Pulmonary tuberculosis, 1st stage.....	7.0-7.5
“ “ 2nd “	6.0-7.0
“ “ 3rd “	4.0-6.0
Laryngeal “	4.0-6.0
Intestinal “	4.0-6.0
Pleural “	4.0-6.0
Peritoneal “	4.0-6.0
Kidney “	3.0-5.0
Bone “	7.0-8.5
Joint “	7.0-8.5
Cutaneous “	7.0-8.5
Glandular “	7.0-8.5

Table I gives the standard dose for adult men, and must be altered according to the general condition of the patient. For instance, patients having high fever, showing a tendency to pulmonary hemorrhage, suffering from neurasthenia, malnutrition, extreme anemia, or showing marked progress of the pathological processes, heart disease, or chronic diseases other than tuberculosis, or presenting a wide tuberculous lesion, etc., should receive smaller doses. The body weight would naturally seem to influence the dose, but my experience has led me to the conclusion that there is no need to vary the dose in proportion to the body weight. However, it must be decreased according to the patient's age; *e.g.*, a boy 10 years old should receive half the dose given to an adult man. The dose for the second injection should be made according to the degree of the reactions produced by the first, as well as by the general condition of the patient at the time of the injection. By a proper dose is meant the amount of the preparation which produces no or only a slight reaction, which disappears 2 or 3 days after the injection, and shows some improvement within 2 weeks. If these results are achieved, the dose should not be altered but should be continued for several injections until a change is deemed desirable. If too great a reaction, *i.e.*, fever exceeding 1°C., is produced, or if a local reaction lasting more than 3 days should occur, the dose must be decreased. If, on the contrary, neither reaction nor improvement is observed, the dose is increased by 0.25 cc. at the next injection. In

severe cases or cases suffering from progressive lesions, the increase must be made with special care.

Interval between Injections.—Great care should be exercised to allow a sufficient interval between the injections, as the interval as well as the dose seems to have much to do in bringing about improvement. The doses shown in Table I are the amounts that should be given once every other week. The injection should never be given with a shorter interval than a fortnight, as otherwise an unfavorable turn in the general symptoms may follow. Takano² reports that he gave lepers large doses weekly or sometimes twice a week, and observed no ill effects. But with tuberculosis such an attempt should not be made. Our experience has convinced us that Koga's view, based on animal experiments, of allowing an interval of 2 weeks between injections is correct. Prolongation of the interval may be made without harmful effects. If, therefore, the reaction produced by the injection should last more than 1 week, the succeeding injection must be postponed.

Reactions and Effects.—Koga has observed that the administration of cyanocuprol may be accompanied by striking reactions. But by diminishing the dose no reaction will be produced, and even if it should appear, no serious symptoms will develop. As a rule, the fever does not rise above 1°C., and the reactions disappear in 2 or 3 days, rarely lasting more than 1 week. The fever is sometimes preceded by a slight chill. Fever does not necessarily accompany the pain in the joints. The general reactions are headache, dullness in the limbs, lack of appetite, etc., and are so slight that no special treatment is called for. A fleeting inflammation appears in the lesion, as pointed out by Koga, but by the improved method of treatment, regional inflammation is avoided. The pulmonary dullness is rarely increased, and if increased it is slight. Râles are often heard, but they disappear in 2 or 3 days with no other treatment than confinement in bed. During the period of reaction the cough and sputum often increase, and if care is not taken to restrain them, hemoptysis may occur. Only one case out of more than 100 cases that I treated suffered from severe pulmonary hemorrhage.

² Takano, R., *J. Exp. Med.*, 1916, xxiv, 207.

Case Reports.

Case 1.—Male; age 43 years. Average build. Family history negative. Infiltration of the upper lobe of the right lung. Pulmonary hemorrhage occurred in July, 1914. A diagnosis of apical tuberculosis was made. The patient has complained of coughing and sputum since Feb., 1915. Temperature 37.5°C. Pulmonary hemorrhage of about 200 cc. took place 2 weeks before admission. Nutrition fair. Anemic. Apex of the right lung dull; medium râles were heard in the same region. 7.5 cc. of cyanocuprol were given at the first injection, and in the evening a pulmonary hemorrhage of about 50 cc. occurred. For 10 days the patient expectorated bloody sputum. After an interval of 2 weeks a second injection of 7.5 cc. was given. This time he presented no ill effects, and rarely expectorated bloody sputum. After five injections he returned to his home. At that time the regional dullness had diminished, and the râles had disappeared. The bacilli in the sputum, which before treatment had been equal to Gaffky's No. VIII, were reduced to No. IV or No. V. The sputum decreased considerably. The patient gained 3.6 kilos in weight.

In one case a severe reaction occurred which resulted in an aggravation of the general symptoms.

Case 2.—Female; age 21 years. Average build. Family history positive. Suffered from infiltration of the left upper lobe of the lung. Right apical tuberculosis. Has always been healthy; no serious illness. The patient suffered from bronchial catarrh, which soon subsided and left no subjective symptoms. Nutrition fair. Face pale. Temperature normal. Pulse more than 90. On the back a dull sound was heard from the apex down to the second intercostal space covering the upper half of the left side of the interscapular region. The right side of the interscapular region had also a slight dull sound. At the left apex a number of consonant râles were heard, and at the right apex a few small râles. 7.5 cc. of cyanocuprol were given at the first injection. On the day of the injection the body temperature rose to 38.1°C. The next evening it remained at 38.4°C., and fell on the 3rd day to 37.4°C. The patient left the hospital against the advice of the physicians in charge. She reported that she had had a temperature of 37.9°C., which became normal in about 2 weeks. No change was observed in the râles and dull sound, but she complained of the sputum which did not occur before the injection. Blood streaks were observed several times in the sputum. The second injection of 7 cc. was made in 2 weeks. This time the dull sound and râles increased slightly, and on the following day the temperature rose as high as 39°C. It was preceded by shivering but no chill. The patient was dismissed on the 3rd day after the injection. Every evening the temperature rose to 38.3–38.4°C., and in about a week pneumonic symptoms developed. The temperature rose as high as 39.4°C. The dull sound and the râles appeared over the whole region of the left lung. These symptoms prevented my attempting further

treatment with cyanocuprol. The patient suffered from extreme emaciation and died in about 3 months.

In this case failure resulted partly from oversensitiveness to the preparation, but chiefly from the refusal of the patient to remain quiet during the period of pronounced reaction, and also to lack of the necessary interval between the injections.

In one case severe pain was caused by the injection.

Case 3.—Male; age 43 years. Average build. Family history negative. The patient was suffering from infiltration of the right upper lobe and left apex, together with laryngeal and intestinal (?) tuberculosis. Has always been healthy; no serious illness. Since Jan., 1915, he has complained of harshness of the voice, with pain in the throat; not conscious of fever. For the past several days he has been suffering from diarrhea,—four or five stools a day,—coughing, and sputum. Appetite poor. Nutrition poor. Severe anemia. Temperature 38°C. Pulse 90. Dull sound over the region of the right apex down to the second intercostal space in front and the lower corner of scapula on the back, from the left apex to the supraclavicular fossa in front and over the corresponding region of the back. Large and small râles heard over this entire region. General respiration sound weak. The bowels are sunken. In the right iliac cavity a hard mass as large as a pigeon's egg is felt, which is not tender. Von Pirquet reaction slightly positive. After the first injection of 6 cc. of cyanocuprol the temperature reached 38.8°C. No change was observed in the lungs and intestines. The pain in the throat subsided for a short time, but reappeared on the 5th day. This time the pain was more severe, and difficulty in swallowing developed. In consequence of severe emaciation the treatment was suspended.

Koga¹ reports a case of intestinal tuberculosis that developed symptoms resembling dysentery in consequence of the injection of cyanocuprol. I have had a similar case.

Case 4.—Female; age 34 years. Average build. Mother died of pleurisy. The patient has the progressive form of pulmonary tuberculosis. Had been healthy until she contracted pneumonia in 1913. In 1914 had pleurisy of the left side, and in Mar., 1915, serous pleurisy of the right side. She catches cold easily, and has complained of harshness of the voice since Mar., 1915, with large quantities of sputum. No diarrhea. Nutrition poor. Face pale, presenting an appearance of cachexia. Temperature 38.2–38.3°C. Pulse 108, regular, thready, and weak. Both apices had a dull sound. Many medium râles were heard at the right apex, over the frontal surface of the left lung and left interscapular region. Respiration sounds weak. The lower margin of the lungs showed no respiratory movement. No change was visible in the heart or the organs in the abdominal cavity. Von Pirquet reaction negative. 0.3 gm. of pyramidone was administered, and the

patient ordered to keep quiet. The temperature became normal in a week, when 6 cc. of cyanocuprol were given. No reaction developed, and the patient was allowed to go home. On the 6th day she ate some indigestible food and diarrhea occurred. Temperature 38°C. Pain in the bowels. On the following day she passed ten pus-like, mucous, bloody stools. No bacilli of tuberculosis or dysentery were found on bacteriological examination. The symptoms subsided in a week, the temperature falling gradually to 37.4°C. In the 2nd week after the first injection she was again admitted to the hospital and 5 cc. of cyanocuprol were given. The temperature, which remained at 37.8°C. before the injection, fell to 37.4°C. on the 4th day after the injection, perhaps in consequence of keeping quiet. After the third injection a severe angina developed and the temperature rose above 39°C. Appetite poor. A fourth injection of 4 cc. was given, and on the 7th day severe cerebral symptoms developed. Patellar reflex normal. Neck not stiff. Kernig's sign absent. The patient died on the 12th day after the fourth injection.

The intensification of the symptoms is not wholly due to the effect of cyanocuprol, but I have reported these three cases in order to show that failures may be encountered. The reactions sometimes appear after a week's delay. In case of such an abnormal reaction, special precautions should be taken. The severe cases and cases suffering from progressive lesions or with a poor prognosis seem especially to suffer from retarded reactions.

Care of the Patient.—Cyanocuprol brings about an improvement in the condition when adequate doses are administered; but this alone is not sufficient, for the condition may be intensified unless special care is taken. Besides the dose of the preparation, which must be regulated for each patient under treatment, care following the injection is essential. By care is meant rest. Disappointments in the past have been explained by the fact that this care had been neglected. Rest would seem to be easy to accomplish, but it is, in practice, one of the most difficult and complex conditions to meet.

It is a well known fact that the psychological condition of the patient influences disease. This is especially true in tuberculosis, for the disease itself is apt to increase the psychic sensibility.

Case 5.—Male; age 36 years. Large build. Family history negative. Pulmonary tuberculosis in the third stage, with intestinal (?) tuberculosis. Contracted pleurisy 8 years ago. Suffered from tuberculosis of the left lung 5 years ago, which gradually spread. In 1914 his case was diagnosed at the hospital

of the Tokyo Imperial University as probable intestinal tuberculosis. Nutrition poor. Slightly anemic. Pulse more than 85, regular. Temperature 38°C. Chest poorly developed. Respiration impaired. Dull sound over the left lung, except the lower lateral part where the sound is nearly normal. Many large and small râles are heard over this region and over the right apex and the right side. Wintrich's phenomenon present at the left subclavicular region. A hardening the size of a pigeon's egg, and slightly tender, is felt at the right iliac region. The first three injections of 5 cc. each were made every other week. The râles decreased and the intestines became less hard. The patient thought he had improved somewhat. 5.75 cc. were given at the fourth injection. On the day before the injection, he received news of the death of his elder sister. In consequence of this, severe emaciation developed and he became utterly helpless. A fifth injection of 5 cc. and a sixth of 4 cc. had no effect, and the administration of cyanocuprol was abandoned.

Case 6.—Female; age 22 years. Small build. Family history negative. Progressive form of pulmonary tuberculosis in the third stage. In her 15th year she was operated on for cervical lymphangitis. Has had no other serious disease. In Feb., 1915, she caught cold and has since suffered from coughing and expectoration. Since April she has been conscious of fever, with sudden increase of coughing and expectoration. Nutrition impaired. Moderately severe anemia. Subcutaneous fat diminished. Skin loose. Pulse more than 114, small, regular, thready, and weak. Cervical glands not palpable. Chest long and narrow. Respiration normal. From both apices to the first intercostal space as well as on both sides of the chest to the fifth rib a dull sound is heard. Throughout the lungs râles are heard, mingled with consonant râles. The lower margin of the lungs has weak respiratory movements. No change is noticed in the heart and various organs in the abdomen. Temperature 38–39°C. Body weight 34.7 kilos. 5 cc. were given for the first injection. No reaction was produced. 5 cc. were given for the second injection, which again produced no reaction. By this time decrease of râles was observed and the temperature became lower. The patient felt better. 4.5 cc. were given for the third injection, after which she ejected bloody sputum. Some members of her family told her about her hopeless condition which distressed her greatly. She was not able to sit up in bed, although by the 5th day after the injection the sputum was no longer bloody. Two more injections were made, but emaciation developed rapidly and she died soon after.

That untoward psychical influences act unfavorably upon tuberculosis has been shown in many cases. Patients who suffer from hypersusceptibility are difficult to treat, and special care must be used in the administration of cyanocuprol.

Rest for the Body.—During the reaction period, the body must be kept absolutely quiet, and the patient must not be allowed to move

about, or severe pneumonia may sometimes develop, as in Case 2. External excitement causes severe reactions which interfere with improvement. Hence while under treatment the patient must be kept under the special care of the physician in the hospital. In the Kitasato Institute the patients are ordered to rest as completely as in relapse in enteric fever. The period of rest varies according to the severity of the disease and other conditions of the patient. For example, the requirement is 3 days for a patient having pulmonary tuberculosis in the first stage, 5 days for the second stage, and 7 days for the third stage. If, however, the patient is suffering from fever, hemorrhage, progressive lesion, retarded reaction, pleurisy, peritonitis, and especially from kidney tuberculosis, the period is considerably prolonged. Even after the expiration of the set period of rest, it is better to keep quiet for another period in order to avoid all danger of fever. Fever or hemorrhage may develop in consequence of a trip by railroad as well as from exercise. The greatest care is demanded at the first and the second injections and no exercise permitted.

Rest for the Lesion.—Rest for the lesion alone produces improvement and, therefore, the splint or plaster bandage is extensively applied for bone or joint tuberculosis. Artificial pneumothorax may also accomplish a similar purpose. Rest for the lesion is an essential element in bringing about complete action of the remedy, and is no less important than rest for the body. The manner of giving rest to the lesion must differ with the form of the disease. The following methods may be indicated.

Pulmonary Tuberculosis.—Coughing and speaking must be stopped. Above all, the cough must be carefully treated, for an increase of the cough often involves danger. Coughing may be satisfactorily controlled by codeine hydrochloride or similar sedatives. To remove the difficulty of expectoration in consequence of tenacity of the sputum, or in nervous coughs, the bronchitis kettle will prove valuable. I usually treat these cases with a solution containing 1 gm. of sodium bicarbonate, 1 gm. of sodium chloride, and 100 cc. of distilled water, by means of a nasal atomizer used by the patient when the coughing returns. Dust must be excluded from the air breathed. Smoking and loud or long speaking must also be prohibited.

Pleurisy.—Breathing is comparatively less harmful in pulmonary tuberculosis, but in pleurisy the movements of the chest rub the lesion. This may cause the greater reaction and less efficacy of the preparation in pleurisy than in pulmonary tuberculosis. In pleurisy, therefore, the patient must not only follow all the necessary precautions required for pulmonary tuberculosis, but the period of rest for the body must be considerably prolonged.

Laryngeal Tuberculosis.—Speaking must be forbidden in cases in which hoarseness exists. Coughing also is more harmful in this condition than in pulmonary cases. Irritating food and smoking must be abstained from.

Intestinal and Peritoneal Tuberculosis.—The peristaltic contractions of the intestine necessarily interfere with the rest for the lesion in intestinal tuberculosis. At first severe reactions were obtained in tuberculosis of the bowels, but these inconveniences have now been eliminated. The precautions taken are briefly as follows: On the day before the injection a laxative such as magnesium sulphate is administered, and on the morning of the injection an enema of saline solution is given in order to evacuate the contents of the bowels. A comparatively less amount of cyanocuprol is then injected. If the patient does not have a stool the next day, an enema or some other treatment should be given in order to insure a daily stool. After the injection no food is to be taken that may produce diarrhea or increase fermentation, and stimulating food accessories or indigestible foods are omitted. Morphine or its derivatives may be resorted to in order to control peristalsis, but they usually cause constipation and consequently incur fermentation, thus leading to stimulation of the intestinal lesions. When a severe enteric reaction arises producing symptoms resembling acute dysentery, morphine may be administered.

Surgical Tuberculosis.—For cutaneous or glandular tuberculosis, no special precaution is necessarily taken except that the lesion should not be exposed to outward stimulation. For bone or joint tuberculosis, a splint or plaster bandage should be applied.

Kidney Tuberculosis.—Similar precautions to those taken in acute nephritis are recommended. For example, stimulating foodstuffs should be strictly prohibited and the patient should be ordered to

take absolute rest. Thus far only a few cases of kidney tuberculosis have been treated.

It is an interesting fact that an intimate correlation between the doses and the rest for the lesion seems to exist. The doses given above have been established by experience. For example, small doses are prescribed in pleurisy, intestinal tuberculosis, and laryngeal tuberculosis; while in surgical cases larger doses are given. The results of the treatment also seem better in the latter than in the former conditions. The difference may possibly be accounted for by the fact that in the former cases, the drug produces severe lesional stimulation which interferes with the improvement. The only practical way of eliminating these unfavorable influences and of establishing improvement is by securing rest for the lesion.

Contraindications.—Koga points out that apricot juice must not be given with cyanocuprol, because of the increase of hydrocyanic acid, while potassium iodide, creosote, guaiacol, and their derivatives, serve to produce severe reactions, and hence all are contraindicated. It is well known that potassium iodide exerts an influence upon tuberculous lesions; for it causes inflammation at the site of the lesion. The precise action of creosote and guaiacol is not yet determined, but it is known that their hypodermic or intravenous administration produces sudden increase of the lesional reaction. All remedies which produce lesional inflammatory effects must be avoided.

Can tuberculin be given coincidentally with cyanocuprol? Koga reports that in a patient that had been treated with tuberculin, cyanocuprol produced a remarkable improvement, while the reactions had been slighter than in patients who had not had tuberculin. But it is better to avoid tuberculin while cyanocuprol is being administered, for the lesion will become sensitive to the various influences. The precise doses of tuberculin and cyanocuprol are not easily established and the combined treatment is not advised. If, however, cyanocuprol should be ineffective, tuberculin may be resorted to after a considerable interval.

The following case is of interest, as it had previously been treated with iodol.

Case 7.—Male; age 49 years. Large build. Mother and wife died of pulmonary tuberculosis. Pleurisy on both sides. Both apices infiltrated. He

has always been healthy and has never had any serious illness. Has been suffering from pleurisy since last year. Temperature had been about 39°C. at first. At present it is nearly normal. Heart frequency increased, and weakness set in. Appetite and nutrition impaired. Constipated. Color pale. Pulse more than 80, regular, medium tension. Dull sound from the apex of the right lung to the first rib in front, and the same region on the back, and at the side of the apex of the left lung. The lower lobes of both lungs have also a dull sound on the back and front. Breath sounds weak throughout. Voice vibrating and weak. On the frontal side of the lungs râles are heard. In the upper lobes on both sides of both lungs bronchial sounds are heard. 5 cc. of cyanocuprol were given at the first injection. Temperature rose to 37.7°C. The next evening it rose to 38.4°C. On the 3rd day it rose to 39.1°C. No unfavorable symptoms were observed in the chest, but the patient complained of pain in the muscles of both hips. Two hard swellings the size of hen's eggs were observed on the left side and one on the right. They were tender and felt like gristle. The patient states that they correspond to the injection points of iodol, which was given 2 months ago, and that they showed no change before cyanocuprol was given. On the 7th day the temperature fell below 37°C., but rose again to 38°C. A second injection of 4 cc. was made 3 weeks after the first. No reaction was produced and the temperature remained below 37.1°C. A third injection of 4 cc. was given 2 weeks after the second. It produced no reaction. The swellings on the hip became smaller,—no larger than a nut. They remained unchanged by the injection of cyanocuprol, and the tenderness disappeared. Symptoms of pleurisy gradually improved. The rise of temperature after the first injection seems to indicate that an intimate relation exists between the two substances.

All the agents used in symptomatic treatment, such as pyramidone, aspirin, codeine, morphine, bismuth chloride, tannigen and its derivatives, ergotine and its derivatives, digitalis and its derivatives, digestive adjuvants, etc., may be given with cyanocuprol. A general diet may also be given except in the cases mentioned.

Prognosis.—The fundamental criteria on which prognosis is based are the same with the cyanocuprol treatment as with other agents. Patients with a noteworthy family history or those in whom there is no von Pirquet reaction except when treated with tuberculin have, as a rule, a bad prognosis. The older lesions apparently are slow to react to the drug. Age seems also to interfere with its action. An acute progressive form of the disease must be treated with special precautions. Even when applied with the utmost care patients suffering from acute lesions have sometimes seemed not to do well under the treatment.

Case 8.—Male; age 37 years. Large build. Family history negative. Progressive form of pulmonary tuberculosis in the first stage. Has always been healthy; no serious illness. Contracted bronchitis in Oct., 1914, from which he recovered in Feb., 1915. In the same month he complained of recurrent bronchitis. Since then he has had moderate coughing and expectoration and sometimes night sweats. Appetite good. One or two stools a day. Nutrition poor. Anemic. Face pale. Two or three swellings as large as peas are present in the cervical glands. The laryngeal mucous membrane is pale. Pulse more than 100, small, regular. Chest long and narrow. Breathing good. Percussion normal. On deep inspiration a few medium râles are heard in the left lung. Respiration sound generally weak. Heart and abdominal organs normal. Von Pirquet reaction slightly positive. The bacilli in the sputum are equal to Gaffky's No. I. The first injection of 7.75 cc. was made when the body temperature was 38°C. It rose to 39°C. the same afternoon. It became normal in 3 or 4 days, and the râles decreased. In 2 weeks crepitations were heard at the third rib in front and in the left scapular region. A second injection of the same dose was given. This time no fever was produced. In 2 weeks, however, the crepitations in the right side of the chest changed to consonant râles. Those on the right side developed moderate consonant râles. A moderate number of râles appeared on both sides. The same dose was given at the third injection. No reaction appeared immediately, but in a week the temperature began to rise and reached 39°C. in 12 days. Râles also increased. At the right apex a dull sound was heard. In 18 days the temperature fell to 38°C. On the 25th day after the last injection the patient received a fourth injection of 6.5 cc. No rise of temperature was observed, but the râles increased. In 2 weeks a fifth injection of 5 cc. was given, and the temperature began to rise. On the 4th day it was 39.4°C. In 2 weeks a sixth injection of 4 cc. was given. The temperature fell this time in a week to 38.3°C., and again rose to 39.5°C. Edema developed on the face and dorsal part of the feet. A slight anesthesia developed at the lips, abdomen, and legs, with slight tenderness in the calves. Heart normal. He probably suffered from beri-beri. A seventh injection of 3.5 cc. was given. No reaction occurred. The symptoms of beri-beri disappeared after 2 weeks of a rice-free diet and treatment with cascara and magnesium sulphate. An eighth injection of 3 cc., a ninth of 2.5 cc., and a tenth of 2.5 cc. were given. Each time no reaction occurred. The râles decreased markedly after the sixth injection. A slight dull sound appeared at the left apex after the seventh injection. Great weakness developed. The patient is still under treatment.

Idiosyncrasy and Accumulative Effect.—A severe case is generally highly susceptible to cyanocuprol. Patients in whom it is difficult to keep the lesion quiet or nervous patients sometimes suffer from severe reactions. There are still others in whom no cause for the

reaction can be accounted for. I have not yet enough data to decide whether they comprise an idiosyncrasy or not.

After the injection of cyanocuprol the lesion becomes susceptible to irritation, but on repetition of the injection no increase in the irritation has been noted. In other words, no case has been met with in which an accumulative effect of cyanocuprol was observed.

Cases in Which Cyanocuprol Did Not Lead to Improvement.

Case 9.—Male; age 33 years. Average build. Family history negative. Infiltration of the left upper lobe; tuberculosis of the right upper and lower lobes. Has always been healthy except for pleurisy in his 16th year and epidemic cerebrospinal meningitis in his 28th year. Coughing for about 1 year. Night sweats. Conscious of fever. Nutrition fair. Face pale. Pulse regular, tension normal. Chest long and narrow. Respiration good. Dull sound present from the apex of the left lung to the second intercostal space in front and the middle of the scapula. Moderate non-consonant râles from the apex of the left lung to the middle of the scapula and over the surface of the left lung in front. The same kind of râles heard over the region corresponding to the upper lobe of the right lung. Maximum temperature 37.2°C. Body weight 49.9 kilos. 7.5 cc. were given at the first injection. 2 weeks later 7.75 cc. were injected. After the second injection many tubercle bacilli were present in the sputum. Sputum has been ejected the same number of times daily as before; *i.e.*, two or three times. Since then 7 to 8 cc. of cyanocuprol have been injected every other week, but no ill effects have been observed. The only change in the symptoms has been a slight decrease of the dull sound in the upper lobe of the left lung, while a slight dull sound has developed at the apex of the left lung and the râles in the left lung have decreased slightly. Tubercle bacilli in the sputum range between 0 to No. VIII of Gaffky's table. A slight rise of temperature was observed after the seventh injection, 37.5°C., rarely 38°C. In this case cyanocuprol had no effect. Body weight lost 3.8 kilos. The patient says he has lost in body weight every summer.

Case 10.—Male; age 33 years. Average build. Had seven brothers and sisters, two of whom died of pulmonary tuberculosis. Pulmonary tuberculosis in the first stage. Has never been strong, but has had no serious illness. In July, 1914, he had hemoptysis. In Jan. and Feb., 1915, the sputum was again bloody. Temperature normal. Sleep interrupted. Appeared generally nervous. Cough and expectoration moderate. Appetite impaired. Nutrition fair. Face pale. Pulse regular, more than 85. Chest moderately developed. Respiration good. No swelling present in the cervical glands. No abnormal dull sound is heard in the chest. A few small râles are heard at the lower margins of both lungs. No abnormal symptoms are present in the heart and the organs

in the abdominal cavity. Von Pirquet reaction weakly positive. Tubercle bacilli in the sputum correspond to Gaffky's No. VIII. 7.5 cc. of cyanocuprol were given at the first injection. A slight increase in the râles was observed the next day, which decreased on the 3rd day. In 2 weeks they could be heard only when he coughed. 7.5 cc. of cyanocuprol were given at the second injection. No reaction. 7.5 cc. were given at the third injection. A slight decrease was observed in the râles which were heard at the time of coughing. No reaction present. For the fourth, fifth, and sixth injections 7.5, 7.25, and 7 cc. were given, respectively. No reactions produced. The bacilli in the sputum decreased to Gaffky's No. II to No. IV. They could not be eliminated. The râles also never subsided. Sleep was interrupted as before. The body weight decreased 2.6 kilos.

Case 11.—Male; age 22 years. Tall and thin. Mother died of pulmonary tuberculosis accompanied by intestinal tuberculosis, and one younger brother died of pulmonary tuberculosis. Pulmonary tuberculosis in the second stage, and intestinal tuberculosis. Has had no serious illness, but is subject to gastro-intestinal disturbances. For 20 days has felt feverish and had night sweats. Coughing and expectoration slight. Appetite impaired. Great emaciation. Face and mucous membrane of the mouth and the eyelids highly anemic. Chest long and narrow. Respiration good. The upper lobes of the right and left lungs have medium râles. Crepitation is heard at the lower part of the right lung. Abdomen is a little sunken. A hard mass as large as a pigeon's egg is felt at the cecum. The region around the navel is tender to the touch. Temperature 37.3°C. Pulse over 90. Body weight 41.8 kilos. The first, second, and third injections consisted of 7, 7, and 6.75 cc., respectively. After the third injection the râles in the left apex increased. The fourth, fifth, sixth, and seventh injections consisted of 7, 7, 6, and 6 cc., respectively. After the fifth injection the temperature rose to 37.5°C., but after that no rise was observed. Once after bathing it rose to 38°C., and at another time after he had eaten ice-cream when he was out of the hospital, it rose to 38.6°C. On another occasion he ate ice-cream while in bed in the hospital and the temperature rose as high as 38°C. For 9 days after the 4th day after the third injection, it ranged between 37.4–38.3°C. At the time of the seventh injection all the râles disappeared except those in the right apex. The hard mass as well as the tenderness around the cecum also disappeared. Dullness remained the same. Diarrhea remained the same as before the treatment; two or three stools daily. Emaciation developed gradually. Body weight lost 6.5 kilos. Bacilli had not been observed in the sputum at the beginning of the treatment but they became visible after the fourth injection and never disappeared. After the seventh injection he was subjected to dietetic treatment and cyanocuprol was suspended, but in spite of the effort to gain in strength, there was no improvement. The temperature remained about 38°C.

Cases in Which Cyanocuprol Produced Some Improvement.

Case 12.—Female; age 23 years. Family history negative. Infiltration of the apex of the left lung. Has been healthy. In 19th year contracted inflammation of the internal ear. 2 years ago she says she contracted pleurisy and intestinal tuberculosis. In Oct., 1914, she contracted tuberculosis of the apex of the right lung. Moderate coughing and expectoration. Occasional night sweats. Temperature 37.3°C. Nutrition fair. Color good. Pulse regular and normal. No swellings present in the cervical glands. Heart and organs in the abdominal cavity normal. Both tonsils enlarged. Mucous membrane of the larynx flushed. Spine curved to the left. Chest medium. Respiration good. A slight dull sound and a few small râles are heard throughout the left lung. Respiration weak at the lower margin of the left lung. The bacilli in the sputum are equal to Gaffky's No. III. Body weight 50.5 kilos. Von Pirquet test strongly positive. 7.5 cc. of cyanocuprol were given at the first injection. The temperature rose to 37.6°C. Coughing increased considerably. The temperature remained at 37.5°C. The same dose was given for the second, third, and fourth injections. No reaction was produced. The temperature fell to 37.3°C. after the second injection. 7.75 cc. were given for the fifth injection. This time slight fever was produced, for it remained at 37.7°C. for about a week, after which it again fell below 37°C. All the symptoms in the lungs decreased markedly after the first injection. Nearly all the dull sound as well as the râles disappeared. Expectoration disappeared after the first injection. No sputum could be obtained for bacteriological examination. Occasional inflammation of the tonsils, but no other complaints. Body weight lost 0.9 kilo.

Case 13.—Male; age 29 years. Average build. Father died of an intestinal disease. Two brothers died of meningitis. One maternal uncle died of tuberculosis. Infiltration of the upper lobes of both lungs. Patient has always been healthy except for pleurisy in his 18th year. Had pulmonary hemorrhage 4 years ago and another attack 4 months ago. At present he coughs and expectorates a little. Color good. No swelling occurs in the cervical glands. Pulse, heart, and organs in the abdominal cavity normal. Temperature normal. Chest poorly developed. Respiration weak. A slight dull sound is heard over the region from the apex down to the first rib in front and the middle of the scapula on the back. Medium râles are heard along the left lung. At the lower part of the left lung a slight dull sound is heard. The bacilli in the sputum correspond to Gaffky's No. III. Body weight 51 kilos. Von Pirquet test weakly positive. 7.75 cc. of cyanocuprol were given for the first, second, and third injections. 7.75 cc. were given for the fourth and the fifth injections, respectively. A slight increase in the râles was observed after the first, third, and fifth injections, and decrease of the dull sound was noticed. The latter remained to a slight degree on the back of both lungs and the apex of the right lung. The râles also nearly disappeared, remaining only on the back of the right lung.

The bacilli in the sputum became so few that in the ordinary film preparation none could be detected. Body weight gained 0.5 kilo.

Case 14.—Male; age 25 years. Father died of tuberculosis. Pulmonary tuberculosis in the third stage. Caries of the fifth rib and tuberculosis of the cervical glands. Has been healthy. In 7th year contracted diphtheria. In 21st year contracted tuberculosis of the cervical glands, and consequently developed anesthesia of both ears. 3 years ago remittent fever developed, ranging between 37 and 39°C. At the same time coughing and expectoration appeared. In April of last year had three hemoptyses, each time losing about 100 cc. of blood. Emaciation. At present the temperature is 37.5–38°C. Occasional hemoptyses. Moderate coughing and expectoration. Emaciation becoming more severe. Von Pirquet test negative. Nutrition poor. Face pale. Lips flushed. Swellings as large as the tip of the little finger present in the cervical glands on both sides. Scars at the left side of the neck and over the fifth costal cartilage on the right are both due to an operation. Closed pustulation as large as a pigeon's egg present at the lower frontal part of the sternum. Pulse more than 90, regular, tension slightly decreased. Chest narrow, especially on the left side. Dull sound over the surface of the left lung. From the apex to the second intercostal space on the right frontal side and the lower end of the scapula on the back is heard a slightly dull sound. Over the whole region where the dull sound prevails and at the region corresponding to the lower lobe of the right lung consonant large and medium râles are heard. Dimension of heart could not be determined. Heart sound normal. Abdomen normal. Body weight 45 kilos. 6.5 cc. were given at the first injection. The following injections were made every other week, each dose being 5 cc. No ill effects appeared. After the fourth injection the temperature did not rise above 37.4°C. The general condition of the patient improved greatly. The dull sound as well as the râles became considerably less. The bacilli in the sputum, which corresponded to Gaffky's No. VIII, never exceeded Gaffky's 0 to No. III. The body weight gained 0.3 kilo.

Case 15.—Female; age 17 years. Average build. An elder sister died of pulmonary tuberculosis. Pulmonary tuberculosis in the third stage, acute, progressive form. Has always been healthy. A year ago suffered from coughing and expectoration, the temperature reaching sometimes as high as 38–39°C., which always subsided in several days. A similar attack occurred 9 months ago and was diagnosed as pleurisy. Severe coughing and night sweats occurred. Nutrition fair. Face pale. Lips cyanotic. Mucous membrane of the eyelids and mouth pale. No swelling present in the cervical glands. Pulse small, regular, and over 90. Chest long and narrow. Respiration weak. The heart beat is conspicuous at the second and third intercostal space. Dull sounds are heard over the surface of the right frontal side of the lung to the second intercostal space on the left and to the lower edge of the right scapula, and over nearly all the surface of the right lung on the back. Many large and medium râles are heard over the whole sur-

face of both lungs except the lower dorsal part. The heart is normal except for a slight hemic murmur. Abdominal organs all normal. Temperature is 38–39°C. Body weight 37.5 kilos. 6.5 cc. of cyanocuprol were given at the first injection. It produced a local reaction. A second injection of 6 cc. and a third of 6.25 cc. were given. 2 or 3 hours after the third injection the temperature rose to 38.4°C., which soon subsided and remained below 37°C. All the symptoms improved considerably. At the fourth, fifth, sixth, and seventh injections, the doses were 6.25 cc. After the fourth injection the temperature did not rise above 37.4°C. Night sweats practically subsided. Severe pathological processes completely checked. At the eighth and ninth injections 6.5 cc. were given. The dull sound and the râles had become considerably less. After the ninth injection the temperature rose to 37.7°C. and resulted in a slight increase of the dull sound and râles. For the tenth injection 5 cc. were given. The patient is still being treated.

Case 16.—Male; age 20 years. Family history negative. Infiltration of the upper lobe of the right lung and peritoneal tuberculosis. In 13th year contracted pleurisy. In 17th year had a little bloody sputum. For 4 months has been complaining of general dullness. Some months ago swelling of the abdomen and pain in the region of the stomach developed. He has been conscious of fever several times a day. No coughing or expectoration. Appetite normal. Stools once every other day; occasional diarrhea. Respiration labored and deep. Nutrition good. Not anemic. Pulse regular and normal. Chest well developed. Slight dull sound is heard at the upper lobe of the right lung. At the right lateral upper part is heard a clear bronchial respiration sound. Many medium râles at the right apex. The right axillary cavity has a dull sound and a few crepitations. Respiration normal at the lower edges of the lungs. Abdomen swollen; right side resistant. In the right iliac cavity is a tender hard mass as large as a pigeon's egg. No exudate is present in the abdominal cavity. Temperature 37.3°C. Body weight 60.1 kilos. 7.75 cc. of cyanocuprol were given at the first injection. On the following day suffered from dizziness; temperature rose to 39.4°C. It fell to the usual point the next day. This is one of the highest febrile reactions that I observed, the temperature varying 2.1°C. A second injection of 7.75 cc., a third of 7.75 cc., and a fourth of 7.5 cc. were given; no reaction followed. After the first injection, the resistance of the abdomen disappeared rapidly. The dull sound of the lung also disappeared, and the râles became fewer. At the fourth injection the symptoms of the lungs and the resistance of the abdominal wall had disappeared completely. The patient did not follow the prescribed diet, and the hard mass in the right iliac cavity became more prominent. He suffered from diarrhea. Body weight lost 1.2 kilos.

Case 17.—Female; age 33 years. Husband suffering from a light case of pulmonary tuberculosis. Caries of the sixth dorsal and the fourth lumbar vertebrae. Infiltration of the apex of the right lung. Patient has always been healthy; no noteworthy illness. 9 months ago she began to complain of general dullness

and occasional fever. No coughing or expectoration. Occasional pain in the left side of the chest. Pain in the back and hips when moving. Appetite normal. No night sweats. Nutrition fair. Slightly anemic. Pulse regular, tension good, more than 78. Right submaxillary glands slightly enlarged. Chest long and narrow. Respiration normal. A slightly dull sound is heard at the apex of the right lung. Crepitations are heard at the second and third intercostal spaces on the left side. The sixth dorsal and the fourth lumbar vertebral processes are tender. Heart and abdominal organs normal. Reflex of knee joint normal. 7.5 cc. of cyanocuprol were given at the first injection. Crepitation increased. The second, third, fourth, and fifth injections were given, the doses being the same as the first. A sixth injection of 7 cc. was given. No reaction developed. The symptoms of the lungs disappeared almost completely, except for a slight weakness of the respiratory sound. A year ago she began to suffer from hiccough, which occurred for 2 or 3 hours daily. This ceased entirely after the third injection. At the same time the pain in the chest disappeared, and there are no other symptoms. She conceived 1 month before the first injection was given. Cyanocuprol had no influence upon pregnancy in this case.

Case 18.—Female; age 28 years. Family history negative. Pulmonary tuberculosis in the second stage and intestinal tuberculosis. Pregnant 7 months. Has always been healthy. A month ago she began to suffer from coughs, fever, pain in the stomach, etc. Diarrhea six or seven times daily. No expectoration. Nutrition poor. Very anemic. Temperature 38°C. Pulse more than 90, regular, weak. Chest long and narrow. Respiration weak. No swelling in the cervical glands. The apices of the lungs and the lower side of the left lung have a slightly dull sound. A tympanic sound is heard at the side of the left apex. Numerous medium râles are heard over the side and front of the left lung. A bronchial respiration sound is heard at the upper frontal side of both lungs and the interscapular region. The abdominal region is swollen and the swollen uterus can be felt. Above the uterus is felt a movable soft mass lying longitudinally. It is slightly tender. In the right iliac cavity there is a tender region. Owing to pregnancy minute particulars could not be determined. Body weight is 42.2 kilos. 4 cc. of cyanocuprol were given at the first injection. After the injection the temperature rose as high as 38.7°C. On the following day it fell to the usual point. The patient complained of a slight pain in the abdomen. No change occurred in the symptoms of the lungs. From the 5th day after the first injection the temperature did not exceed 37.2°C. Diarrhea decreased to one or two times daily. Abdominal pain also subsided. 5 cc. were given for the second injection. No reaction occurred. Diarrhea stopped. A third injection of 5 cc. and a fourth of 4.5 cc. were given. The temperature rose to 37.4°C., and fell to 37°C. on the 3rd day. The dull sound decreased a little but no change occurred in the râles. As labor approached the treatment was suspended. Cyanocuprol again produced no harmful effect on pregnancy. The intestinal tuberculosis improved greatly, but the pulmonary symptoms remained unimproved.

I deem it proper to state here that the cases which have improved and which ceased to receive further treatment have been examined afterwards from time to time, and thus far have rarely relapsed. Moreover, those that had some slight symptoms left when they ceased to receive cyanocuprol were found to have continued to improve without receiving further medical treatment. I have seen no case in which the symptoms increased after the completion of the treatment with cyanocuprol.

SUMMARY.

Cyanocuprol is markedly effective in tuberculosis, and we believe that it will play an important part in clinical medicine. It may be used more generally than tuberculin.

The amount of the dose is closely related to the reaction and the final results. It should be determined for each patient after a careful examination of his symptoms. The maximum dose of 8.5 cc. should in no case be exceeded.

The shortest interval between injections should be 2 weeks. If the drug is given after a shorter interval, no improvement is observed and the effects are sometimes dangerous.

In order to obtain the best results the patient should be placed under conditions of complete physical and mental rest after the injection; this applies even to light cases. Care should also be taken to secure rest for the lesion.

During the period of the treatment irritants to the lesion, such as potassium iodide or tuberculin, should be avoided; apricot juice, guaiacol and its derivatives, and iodol are contraindicated.

No marked idiosyncrasy has been noted and no accumulative effects have been observed.

I desire to express my indebtedness to Dr. Kitasato for privileges in connection with the execution of the present work and to Dr. Koga and Mr. Nemoto for suggestions and assistance.