A CONTRIBUTION TO THE CHEMOTHERAPY OF TUBERCULOSIS.

FIRST CLINICAL REPORT.*

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In the previous paper I have presented data on the specific chemotherapeutic treatment of experimental tuberculosis with my preparation of copper cyanide, called Liquid D. I desire now to present some of the results of the application of the treatment to human cases of tuberculosis. The treatment was first applied on September 26, 1914, at the Imperial Institute for the Study of Infectious Diseases, at which time Professor Kitasato was still its director. When he left the Institute on November 6 of the same year and established the Kitasato Institute for Infectious Diseases I followed him to the new institution where the treatment has been continued. In all, sixty-three treated cases are included in this report. The results have been tabulated as follows:

TABLE I.

<table>
<thead>
<tr>
<th>Class</th>
<th>Total No. treated</th>
<th>Cured</th>
<th>Improved</th>
<th>Died</th>
<th>Treatment suspended</th>
<th>Under treatment</th>
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</thead>
<tbody>
<tr>
<td>Non-active tuberculosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1st stage</td>
<td>19</td>
<td>13</td>
<td>2</td>
<td></td>
<td>1</td>
<td>3</td>
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<tr>
<td>2nd &quot;</td>
<td>6</td>
<td>3</td>
<td>3</td>
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<tr>
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<td>5</td>
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<td>2</td>
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<tr>
<td>3rd &quot;</td>
<td>8</td>
<td></td>
<td>3</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Surgical tuberculosis</td>
<td></td>
<td>1</td>
<td>4</td>
<td></td>
<td></td>
<td>2</td>
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<td>25</td>
<td>22</td>
<td>3</td>
<td>4</td>
<td>9</td>
</tr>
</tbody>
</table>

*The original paper in Japanese was read before the Alumni Meeting of the Kitasato Institute for Infectious Diseases, Tokyo, Apr., 1915.
The term "cured" is applied to the cases that gained in body weight, showed temperatures below 37°C., no or nearly no physical signs, and bacillus-free sputum, though before treatment the sputum abounded in bacilli; and the patients did not complain and could attend to their regular work. This class of patients is being examined monthly at present in order to determine the permanence of the cure. The term "improvement" is applied to those cases that are still under treatment or in which treatment has been discontinued; they have gained in body weight, and show temperatures below 37°C., while bacilli are occasionally found in the sputum, and other symptoms are still present. "Under treatment" is applied to cases which are at the beginning of the treatment and in which the influence of the preparation is not yet evident. One of the patients classed as active tuberculosis in the second stage has passed into the third stage, in consequence of lack of nourishment preceded by hemoptysis.

I shall describe briefly the effect of the preparation upon the lesions and upon the patients, before reporting the typical cases.

**Influence of Liquid D upon the Lesions.**

In one case of acute progressive pulmonary tuberculosis, which had been negative to the von Pirquet test, the preparation produced no effect. But in other cases of pulmonary tuberculosis, there appeared, on the day following the injection, dullness accompanied by râles; if the dullness and râles were present before treatment, the former became more distinct, and the latter increased. These changes are indicated in the chest charts (Cases 7 and 9), and they disappear or diminish on the 8th or 9th day after the injection. By repeated injections the regional reactions gradually disappear or diminish, but by increasing the dose of the preparation they reappear. With each successive disappearance of the signs physical regional phenomena also diminish, until finally they disappear altogether. The dullness at the site of the old lesions does not always disappear; sometimes it is converted into a short tympanic sound. In a few cases the dullness as well as the râles diminish or disappear immediately after the first injection. In Case 2 and in five other cases it was difficult to detect the regional sign before injection, but on the day following the injection râles and dullness appeared by which the lesions could be easily detected, as is depicted in the chart. From these reactive phenomena, as well as from the animal experiments, we have concluded that congestion occurs in a high degree about the lesion immediately after the injection of the preparation. However, in four cases in which bloody expectoration was present, the preparation produced no injurious effect upon the bleeding; and in two of the
four bleeding ceased on the day after the injection. The cases in the third stage generally show stronger reactions, which sometimes last as long as 2 weeks.

In cutaneous tuberculosis a local hyperemia and edema arise in a few hours after the injection. In one case pustulation of the lesion was observed 24 hours after injection. These reactions usually disappear in from 8 to 9 days, and at the same time the lesion diminishes greatly in size. With repetition of the dose the reactions diminish until at last they do not appear at all. Therefore, the minimum dose should first be given, and increased by 0.5 mg. each time subsequently. In this way the same degree of reaction may be obtained each time.

Five cases of tuberculosis of the lymphatic glands have been treated. One patient suffered from slight pain at the site of the lesion, but no swelling was observed. After two injections the lesion was completely absorbed. One case suffered from severe pain immediately after the injection. The gland became swollen considerably and ulcerated on the 2nd day. The remaining three cases suffered from swelling in the region of the gland, and pain on the following day, which disappeared in 7 to 8 days. In two of the three patients, four injections have led to the complete absorption of the lesion, while in the remaining case a hard nodule the size of the tip of the small finger, and feeling like cartilage, remains.

In one case of tuberculosis of the kidney (Case 3), the upper part of the left kidney was found on palpation to be swollen to the size of the fist. On pressure hyperesthesia and hematuria were observed. The latter ceased on the 2nd day, while the swelling and pain disappeared on the 7th day after injection. With the subsidence of the pain at the time of urination, the urine became markedly clearer than before treatment. Unfortunately the patient ceased to come for treatment after the second injection.

One case was suffering from vertebral caries with open suppuration accompanied by pulmonary tuberculosis in the first stage and tuberculosis of the lymphatic glands. The patient complained of oppressive feeling in the breast cavity after each injection. After twelve injections the patient was relieved of discomfort and was able to return to work.

In two cases of intestinal tuberculosis, the injection brought about a temperature of 40°C. with ten to twenty bloody mucous diarrheal stools 3 days later. These phenomena disappeared in 2 days. Three more cases of intestinal tuberculosis were subjected to the special precaution of evacuating the contents of the bowels beforehand, and thus these inconveniences were avoided.

Eighteen cases that had been receiving tuberculin and vaccine treatment according to Shiga's method showed neither local reactions nor rise of body temperature. The duration of the disease was considerably shortened. Case 6 is typical of these cases.
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Influence upon the Tubercle Bacilli in the Sputum.

A bacteriological examination was made of the first sputum expectorated each morning in six cases in the second and third stages. The results have been recorded according to Gaffky's table and arranged diagrammatically in curves (Text-figs. 1 to 6).

In Case 2 a remarkable increase was observed from the day following injection. The climax was reached on the 10th day. From the 11th day, however, a gradual decrease was noted, and negative results were obtained on the 14th day. On the second injection of the preparation and afterwards, a slight increase was observed each time, but from the 10th day a decrease was noted. At present negative results are always obtained even after the injection. In Case 3 the decrease was observed immediately after the injection. Negative results were obtained in 2 weeks. The patient ceased to receive the treatment after that day, and has not reported since. In Case 5 the decrease was observed immediately after the first injection. Negative results were obtained from the 8th to the 14th day, when the second injection was given. On the day following the second injection, an increase to No. II of Gaffky's table was observed, but on the 3rd day negative results were obtained. Since that time two injections have been given with negative results on each examination. In Case 8 innumerable bacilli appeared on the day following the injection, but they decreased to Gaffky's No. II on the 14th day. The second injection again resulted in the appearance of innumerable bacilli. A remarkable decrease was observed from the 9th day, and at last on the 14th day negative results were obtained. From the day following the third injection a gradual increase was observed until the climax was reached on the 9th day. Since then a gradual decrease has been noted, and negative results were obtained on the 14th day. Each examination after that gave a negative result, although five injections have been made. Case 9 was in the third stage of pulmonary tuberculosis. On the 3rd day after the first injection a great increase in the number of bacilli was observed. From the 5th day they decreased, but on the 11th day innumerable bacilli were observed for the second time. They decreased on the following day. After the second injection a gradual increase of the bacilli was noted, and no decrease was observed. The fourth and the fifth injections had no effect. The physical phenomena grew worse, the temperature curve did not fall, and the fever reaction became permanent. No further treatment was given on account of weakness. Case 10 also belonged to the third stage. On the 3rd day after the first injection, innumerable bacilli appeared, but on the 5th day a gradual decrease was observed. On the 9th day negative results were obtained, but from the 10th to the 14th day innumerable bacilli were again observed. The results of the examination on the 13th day were negative, as the material for examination was unsatisfactory, and they are therefore not given in the chart. The second injection gave a better result, and the third resulted in a slight increase on the day following the injection.
A gradual decrease was observed and a negative result finally obtained. After that four injections were always given, the dose being increased each time. The dose was then decreased slightly, and at present a negative result is nearly always obtained.

The film method of bacteriological examination of the sputum is liable to error, for the concentration of the specimen, the thickness of the film, and the material selected produce different results. The more exact antiformin treatment of the sputum is, therefore, to be preferred. As the examination of the first morning expectoration for several days in succession gives important data as to the effect of the preparation, I chose certain cases upon which these successive examinations were carried out. The results were found to correspond with the changes of the local reactions and the temperature curves. One of the phenomena that should be especially noted is that a patient in the first stage of pulmonary tuberculosis who ejected no bacilli in the first sputum on the day of the injection, often passed as many bacilli as correspond to Gaffky’s Nos. II and III on the 2nd and 3rd days after the injection. To a patient in the third stage of the disease, a large dose either exceeding or the same as that given to a patient in the first or second stage results only in an intensification of the symptoms or an increase in the number of bacilli. Changes in the form of the bacilli were observed on the 2nd or 3rd day after the injection. The bacilli will then present the following three varieties: (a) the granules in the bacilli become indistinct and thus the interior becomes somewhat homogeneous; (b) the bacilli which have divided into several sections resemble streptococci; (c) the bacilli which have collected in large masses resemble staphylococci.

The three degenerated forms of the bacilli are often visible when cavities are present in the lung or the specimen has been overheated for staining purposes, and special precautions must therefore be taken before the examination is made. If the bacteriological examination of the patient in the first stage shows that the bacilli in the sputum are normal, the bacilli of the same case after the first injection will be degenerated forms similar to those often discovered in the sputum of patients having lung cavities. It may be conjectured that this degeneration in the form of the bacilli is produced by the injection
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of the preparation. The sputum will, however, contain normal bacilli again 5 weeks after injection. The transformation gradually sets in, beginning with the 2nd or 3rd week.

Influence upon Body Temperature.

In more than twenty cases in which the body temperature ranged between 37° and 38°C. before injection, the temperature subsided completely after one or two injections and did not rise again above 37°C., as shown in the temperature curve of Case I.

The curve of Case 4 shows that the temperature which previously ranged between 38° and 39°C. gradually fell after the first injection, and after the second did not rise above 37°C. This was a case of pulmonary tuberculosis in a woman in the third stage, with great weakness. She showed general improvement in consequence of the reduced temperature, and was therefore dismissed from the hospital. Unfortunately she had a chill the same night and her temperature rose to 40°C., due to a pneumonic attack, which subsided after complete rest, the temperature falling again to 38°C. The lesion, however, was observed to have extended considerably. The third injection brought about no improvement, and the patient died of debility. From this it will be seen that patients suffering from pulmonary tuberculosis in the third stage should be kept quiet for a period of 2 weeks after the injection. In three cases in which there had been no rise of temperature, it rose to 38-39°C. after slight exercise within 3 or 4 days after the injection. A localized pneumonic attack also occurred in these cases, but subsided after rest of about 3 days. Hence I emphasize the fact that in cases of slight pulmonary tuberculosis the patients must be kept quiet for 3 to 4 days after each injection.

Case 3 had a febrile attack on the 3rd day after the first injection (the dose being 16 mg.), in spite of having been kept quiet. After the second injection (same dose) the temperature rose only to 37.7-38°C., and the third injection (15 mg.) was not followed by fever.

Case 8 was given 15 mg. for the first injection. The temperature became normal.

Case 9, as already described, had a severe local reaction.

Case 10 was one of pulmonary tuberculosis in the third stage, the temperature reaching 39.8°C. Three injections of 16 mg. each were given, followed by a normal temperature and improvement of the physical signs. The bacilli in the sputum became considerably less. With the hope of accelerating the favorable effects 17 mg. were given for the fourth injection. There followed increase of the bacilli in the sputum and rise of temperature above 38°C. After 3 weeks’ rest in bed the temperature fell to normal, after which the fifth and then the sixth injection, each consisting of 16 mg., were given. The temperature remained normal, the physical phenomena improved, and the bacilli in the sputum almost
disappeared. As a result of this experience we believe that the dose and the interval between each two injections should be governed by special precautions. Reduction of the dose to 13 mg. in cases suffering from pulmonary tuberculosis in the third stage, and in cases of spreading pulmonary tuberculosis followed by pleurisy (Case 9), produce, as a rule, no rise of temperature, but rather a reduction to normal. Drs. Otani, Okawara, and Yabe are carrying on clinical observations of various kinds in the Kitasato Institute, in order to learn the variety and nature of the reactions and the manner of their control. I have also asked more than twenty specialists in Japan to use my preparation, and reports from these sources may therefore be looked for. In three cases the temperature began to rise on the 10th day after each injection. It has not yet been determined whether the next injection in these cases should be made on the 11th day.

Influence upon Body Weight.

During the 3 days after injection, decrease of the body weight, amounting to 0.5 to 1 kilo, was observed in cases of the first or second stage. But before the next injection, or in 11 days, the weight will again rise to the point present before the injection, and usually even higher. However, with the cases showing a certain intensity of reaction, or in the third stage, the loss following the injection may not be regained. This result might perhaps be avoided, if more time were allowed between each two injections. Among the sixty-three cases which I have treated, a loss of weight has been observed in six only, while all the rest gained more or less.

Influence upon the von Pirquet Reaction.

Three cases in which the von Pirquet reaction was fading were given the preparation with the result that the regional infiltration reappeared and swelling was produced. In one case a blister was formed, which disappeared in 2 or 3 days. This phenomenon may indicate that the preparation has a certain action upon the toxin of the tubercle bacillus.

Thirteen cases that had given positive von Pirquet reactions were reexamined from 2 to 3 months after the disappearance of all clinical and bacteriological signs, and all were negative.

Influence upon the Subjective Symptoms.

A marked improvement is often produced in cases of pulmonary tuberculosis in the first or second stage, while in the third stage severe fatigue is felt for 3 or 4 days. Sometimes cases in the first or second stage also suffer from fatigue. At the same time a slight flush or night sweat may result, which disappears in 2 or 3 days.
Directions for the Use of the Preparation.

As a result of the experimental tests in animals on the toxicity of the preparation, I have come to the conclusion that 0.6 gm. may be introduced without injury into the veins of a man weighing 60 kilos. Moreover, it was found that a dose sufficient to establish complete cure in the experimental tuberculosis of the guinea pig is 0.5 mg. per 500 gm. of body weight. Hence, a curative dose of the preparation for a man seems to be 0.1 gm. The great difference in the species of animals was, of course, taken into consideration, and therefore in the beginning I gave a dose of 10 mg. to human cases.

Dr. Kojima, who had been suffering from pulmonary tuberculosis for 10 years, offered himself for the first trial of the preparation; he developed ileus and strangulation of the intestine and died before the influence of the preparation could be seen. The test proved, however, that in the dose employed the preparation was non-toxic for man.

The preparation is colorless, transparent, and of neutral reaction. If allowed to stand in the air for more than 6 hours, crystallization sets in. It must therefore be used as soon as the ampules are opened.

The preparation is highly irritating to the tissues and hence neither subcutaneous nor intramuscular injection can be employed and it must be injected exclusively into a vein. Injected into the subcutaneous tissues or muscles it causes severe pain and swelling. After injection the patient must be kept absolutely quiet in bed until the reactions disappear. As a rule, 3, 7, and 14 days are the periods during which patients in the 1st, 2nd, and 3rd stages, respectively, of pulmonary tuberculosis must keep quiet. Extreme emaciation is a contraindication to the employment of the preparation.

Rest of the organs affected by tuberculosis is also necessary; e.g., the lessening of the amount as well as the choice of food in intestinal tuberculosis, the application of narcotics for the prevention of hemoptysis in pulmonary tuberculosis, the application of narcotics for the purpose of decreasing cough and limitation of speech in laryngeal tuberculosis, production of artificial pneumothorax (probably) in pleural tuberculosis, and application of splints for surgical tuberculosis.

Rest is necessary because the injection causes local congestion and
therefore bleeding may occur; but, on the other hand, the injection
has been shown to increase the coagulation of the blood, and conse-
quently hemorrhage will stop if rest is maintained. The injection
should be made slowly, otherwise it may cause acceleration of the
heart action and giddiness.

Dose.—The primary doses for the various stages and types of tuber-
culosis are as follows:

<table>
<thead>
<tr>
<th>Tuberculosis Type</th>
<th>mg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary tuberculosis 1st stage</td>
<td>14–16</td>
</tr>
<tr>
<td>&quot; 2nd stage</td>
<td>12–14</td>
</tr>
<tr>
<td>&quot; 3rd stage</td>
<td>8–12</td>
</tr>
<tr>
<td>Intestinal tuberculosis</td>
<td>8–12</td>
</tr>
<tr>
<td>Laryngeal</td>
<td>8–12</td>
</tr>
<tr>
<td>Pleural</td>
<td>8–12</td>
</tr>
<tr>
<td>Peritoneal</td>
<td>8–12</td>
</tr>
<tr>
<td>Tuberculosis of lymphatic glands</td>
<td>15–17</td>
</tr>
<tr>
<td>&quot; bone</td>
<td>15–17</td>
</tr>
</tbody>
</table>

The doses for cutaneous tuberculosis should be increased each time by 0.5 mg.
from the second injection. For laryngeal tuberculosis, however, decreasing by
0.5 mg. after the second injection is better. For other types of tuberculosis the
problem of whether to increase or decrease, to repeat the increase and decrease,
or to maintain the same dose is still to be worked out.

When the fever reaction lasts more than 2 weeks, it may often be reduced
by lessening the doses by 1 mg. for the subsequent injection.

For pregnant women a little smaller dose should be given.

In intestinal tuberculosis purgatives must be given on the day previous to the
injection.

An interval of a fortnight has been regularly allowed in every case. I have
had no instance in which even a small amount of the preparation was injected
at shorter intervals.

The preparation is affected by phenol and lysol. Therefore the
skin and syringe must not be disinfected with these solutions. The
instruments must be disinfected by heating, then dipping in alcohol,
and washing carefully with physiological saline solution. The skin
should be disinfected with tincture of iodine and alcohol.

Internal administration of apricot juice will increase the free
prussic acid in the body, and it should therefore not be given with
the preparation. Creosote and its derivates and potassium iodide
sometimes produce fever and other ill effects.
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Fastness of the Bacilli.—An emulsion of the organs of Treated Animals 134 and 135, which had been receiving injections of the preparation, was introduced into the peritoneal cavity of a guinea pig. Tuberculosis of the intestine and spleen, with nodule formation, was produced. By injecting Liquid D, the nodules were made to disappear. I observed a case in which the preparation was given intravenously over twenty-one times to a patient who is now improving. These facts may show that the preparation probably brings about no fastness in the tubercle bacilli.

Brief Case Reports.

Case 1.—T. F., female, aged 18 years. No information obtained about grandparents, who died when she was a child. Her father died of beri-beri in his 40th year; mother living; three brothers and sisters, one of whom died of a disease of which she knows nothing. No tendency to tuberculosis seemed to exist. She had always been healthy and free from severe illness, except diphtheria, which she contracted in her 7th year. She suffered from a slight swelling and tenderness of the bowels in Apr., 1914. The condition, which was diagnosed by the attending physicians as peritonitis, subsided in about a month. She had been well since then until the middle of Oct., 1914, when she caught cold and suffered from fever and cough.

Diagnosis.—Pulmonary tuberculosis in the second stage; serous pleurisy on left side.

Present Illness.—Weak constitution; malnutrition; skin not dry, elasticity normal; poor in subcutaneous fatty tissue; face pale; conjunctiva anemic; larynx slightly red; no swelling in the lymphatic glands of the neck; typical pigeon chest; breathing weak on the left side; percussion sound short within the region of four fingers' breadth at the apex on the right back; left lung, dullness below the third rib; on the left frontal apex and right lateral apex rales were heard; respiration weak, lacking in the vocal vibration; bowels normal; pleural lymphatic glands, no swelling or tenderness; body weight 33.2 kilos. Von Pirquet reaction, +, +, +.

Progress.—On Nov. 10, 1914, 15 mg. of the preparation were injected intravenously. From the following day the fever subsided and the general condition improved. The bacilli correspond to Gaffky's No. II. Since then twenty injections have been given. At present the patient weighs 35.2 kilos; has a dullness over the right apex; and the sputum is free from tubercle bacilli.

Case 2.—K. K., male, aged 29 years. Parents and six brothers and sisters all living and healthy; no congenital tuberculosis. Has always been weak and

neurasthenic, but has had no severe illness except colds. 4 years ago he swallowed a piece of metal, which was removed by operation. 2 years ago a diagnosis of tuberculosis of the right apex was made. At that time the temperature was above 37.4°C., and negative results had been obtained by bacteriological examination of the sputum. Under clinical treatment all the symptoms subsided in about 3 months. In Jan., 1914, he suffered from a febrile attack, the temperature reaching as high as 38°C., with pain in the left thorax. Toward the end of the month, the fever reached 40°C. with accompanying expectorations, cough, and night sweats. Appetite unimpaired; stools once daily.

**Diagnosis.**—Pulmonary tuberculosis in the second stage.

**Present Illness.**—Constitution medium; nourishment good; skin not wet; features anemic; cheeks slightly flushed; conjunctiva anemic; no white membrane over the tongue; neck a little long; lymphatic glands of the neck not swollen; thorax normal in form; breathing weak along the left side of the thorax; by percussion on left upper lobe, above the line corresponding to the second intercostal space, dullness is observed; on auscultation rales are heard over this area; right upper lobes, bronchial sound; at the apex of the heart and left axillary region slight friction; general respiratory sounds coarse; dullness over the region of the heart; heart normal in size; heart sounds also normal; all organs in the abdominal cavity normal; urine showed no casts or albumin. Von Pirquet reaction, +++, ++, +. Bacilli correspond to Gaffky's No. IV. Body weight 53.3 kilos. Temperature 37.4°C.

**Progress.**—Received intravenously 16 mg. for the first time on Feb. 26, 1915. On Feb. 28 febrile reaction reaching 38.3°C. On Mar. 3 it reached as high as 39°C. Afterwards it fell to 37.6-37.7°C. The behavior of the bacilli in the sputum is shown in the chart; after an interval of 2 weeks the second injection was given. The temperature began to fall, the highest being 37.3°C. Six more injections each at intervals of 2 weeks were given. At present the temperature is 37°C. On the left side of the intercostal space one or two rales are heard; no dullness or bronchial respiration along all the remaining regions of the lungs. The bacilli correspond to Gaffky's No. II. The patient is still receiving the injection. Body weight 53 kilos.

**Case 3.**—T. Y., male, aged 25 years. Both parents healthy; three brothers and sisters living; two brothers died of consumption. The patient has never been strong. 3 years ago he caught cold and suffered from cough and expectoration, and very severe night sweats and fever, which improved considerably under the use of the preparation for 4 months. From Nov., 1914, a renewed attack of fever was observed. He suffered this time from hematuria; urinated fifteen times in 24 hours. He also had a severe pain at the opening of the urethra and in the lower bowels. At that time he urinated over seventeen times daily. Appetite impaired.

**Diagnosis.**—Catarrh of the left apex and tuberculosis of the left kidney.
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Present Illness.—Constitution and nourishment impaired; skin dry; features emaciated; conjunctiva highly anemic; pulsation 110, weak; neck long; no swollen lymphatic glands; thorax symmetrical; breathing slightly weak on the left side; on percussion over the left frontal region of the lung there were dullness down to the third rib, and bronchial respiration and metallic respiratory sounds; over the whole region of the upper lobe of the left lung there were slight râles; normal precordial dullness; anemic heart sounds; left kidney slightly tender and impalpable; bladder not tender; the bacilli corresponded to Gaffky's No. III. The tubercle bacilli in the urine were moderately numerous. Urine neutral and slightly cloudy; considerable deposits were obtained by centrifugalization; albumin in the filtered liquid; no epithelial cells visible under the microscope. Von Pirquet reaction negative. Weight 35.4 kilos. Urine 1,450 cc.; urinated fifteen times daily.

Progress.—On Feb. 9, 1915, 15 mg. of the preparation were injected intravenously. On the following day the left kidney was found to be tender and as large as the fist. The urine assumed a red color, erythrocytes being present; amount 1,700 cc.; urinated fourteen times. On Feb. 11 the pain in the lower bowels and at the urethral opening at the time of urination disappeared, while the urine became somewhat limpid. The deposit obtained by centrifugalization was examined microscopically, and tubercle bacilli were demonstrated. The symptoms in the lungs showed no conspicuous changes. The bacilli in the sputum are shown in the chart. Since that time the urine increased to 2,000 gm. He left the hospital and has not reported since.

Case 4.—I. O., female, aged 19 years. Father died of stomach trouble; mother and one younger brother living. No evidence of an inherited tendency toward tuberculosis. She had been healthy without any noteworthy illness since birth. She suffered from cough and night sweats since Dec., 1914. Menstruation irregular; appetite impaired; sleeps well.

Diagnosis.—Pulmonary tuberculosis in the third stage, and on the right side tubercular pleurisy.

Present Illness.—Constitution good; nourishment impaired; features agonal; cheeks flushed; conjunctiva highly anemic; skin dry; tongue has no white membrane; pulse weak, count over 105 per minute; temperature 38.1°C.; thorax symmetrical; respiration weak on the right side; right lung shows bronchial respiration down to the fourth intercostal space; right side of the back has a short sound, and on auscultation bronchial sounds with râles; right apex measures 4 by 3 cm.; normal precordial dullness; heart normal; lower bowels somewhat distended; axilla is tender, but has no dull percussion sound; no hypertrophy of the intestinal walls or lymphatic glands occurs. Von Pirquet reaction, +, +, −. The bacilli correspond to Gaffky's No VII. Body weight 43.8 kilos.

Progress.—Received intravenously 16 mg. of the preparation on Feb. 16, 1915. The body temperature fell to 37.5°C. on Mar. 1. General condition improved. Received the second injection of 16 mg. on Mar. 3. The temperature rose to 38.1°C. and fell again to 37.1-37.2°C. on the following day; general conditions
improved markedly. She was dismissed from the hospital on the 6th day after the second injection. On that evening fever set in which rose to 39.8°C at 9 o'clock, caused by overexertion. Since that time emaciation became conspicuous, and the temperature curve became irregular. She was again admitted to the hospital. The third injection was given on Mar. 19, and the fourth on Apr. 7, each time the doses being 16 mg. No reduction of fever was produced. Appetite poor. Died on Apr. 28.

**Case 5.**—M. K., male, aged 27 years. Both parents healthy. No inherited tendency to tuberculosis could be traced. He contracted measles in his 2nd year, but besides this he has had no marked sickness until 4 years ago when he suffered from an external wound and a broken right fifth rib, followed by an attack of pleurisy which yielded to medical treatment. 2 months ago hemoptysis (about 299 cc.) occurred. Since then he has had several hemorrhages. He is suffering from cough, with moderate expectoration, but no night sweats. Appetite good. Stools once daily.

**Diagnosis.**—Pulmonary tuberculosis in the second stage; right tubercular pleurisy.

**Present Illness.**—Constitution and nourishment good; conjunctiva not anemic; pulse regular, 84 per minute; no jugular lymphatic gland swelling; thorax symmetrical; breathing weak on right side; on auscultation râles were heard; at the frontal border line between the right lung and the liver an inspiratory bronchial sound was heard; on the back corresponding to the lower margin of the scapula a short friction sound; the left apex had a short sound at the region corresponding to the fossa supraclavicularis; normal precordial dullness; heart sounds also normal; no change in the bowels. Von Pirquet reaction, +, +, +. The bacilli correspond to Gaffky's No. V. Temperature 37.5°C. Weight 49.1 kilos.

**Progress.**—The first intravenous injection of 16 mg. of the preparation was given on Jan. 8, 1915. A night sweat occurred the same night. On the following day along the border line between the right lung and the liver numerous râles were heard, but the friction sound on the back of the right lung disappeared; during the night of Jan. 12 he suffered from pulmonary hemorrhage (about 30 cc.). Since that night until Jan. 22 he has had several hemorrhages; bloody sputum was expectorated until Jan. 29. Therefore the second injection was postponed until Feb. 2, when 16 mg. were again given intravenously. The general condition showed great improvement. The third injection (16 mg.) and the fourth (17 mg.) were given on Feb. 18 and Mar. 5, respectively. The symptoms in the lung disappeared completely, and the sputum was free from tubercle bacilli. Subjective symptoms also subsided. Body weight increased to 49.8 kilos.

**Case 6.**—M. J., male, aged 34 years. Father died of heart disease; mother living. Has no paternal uncles or aunts; three maternal uncles and aunts, one of whom died of carcinoma. Three brothers and sisters. His elder brother died of tuberculosis and his nephew is also suffering from it.

He has been weak since birth, but has contracted no serious disease. In Apr., 1915, he was found to be suffering from pulmonary tuberculosis. Since that
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Case 1.—J. C., male, aged 24 years. Father and mother both died of pulmonary tuberculosis at 40 and 30 years, respectively. He had one brother who died of tuberculosis; the rest are living. He was always healthy. In 1913, while in a state of affairs, a diagnosis of tuberculosis of the left lung was made; he had no cough or expectoration; the following year he was treated with climatic and tuberculin; he says he is susceptible to colds; at present little expectoration. Appetite normal; stools once daily. 

Diagnosis.—Pulmonary tuberculosis in the second stage.

Present Illness.—Both constitution and nourishment good; skin and subcutaneous tissue give no sign of anemia. Larynx somewhat reddened; no swelling in the jugular lymphatic glands; thorax symmetrical; breathing also symmetrical. In the left lung short percussion sound down to the third rib in front and the lower edge of the scapula on the back; these regions had a weak respiratory sound while at the apex a bronchial respiratory sound was heard; the right apex has a short sound over a radius of four fingers; normal precordial dullness; bowels normal; temperature 36.9°C. Bacilli in the sputum correspond to Gaffky's No. 1. Weight 36.3 kilos.

Progress.—The first intravenous injection of 16 mg. was given on Nov. 10, 1914. The left apex had a dull percussion sound, and râles appeared. Weight on Nov. 24, 36.3 kilos. On the same day the second injection of 16 mg. was given. Weight on Nov. 26, 35.8 kilos; on Dec. 8, 36.1 kilos. On Nov. 8 he had only a very weak respiratory sound at the left apex; all other symptoms absent. On Jan. 12, 1915, he was examined, but had no symptoms. The sputum also was found to be free from bacilli. On Apr. 9 body weight was 47.5 kilos. Von Pirquet reaction negative. No physical phenomena were present in the lung. No subjective symptoms.

Case 7.—S. K., male, aged 36 years. Father and mother both died of stomach trouble at 71 and 67 years, respectively. Six brothers and sisters, one of whom died of tuberculosis; the rest are living. One maternal relative is suffering from tuberculosis.

He has never been strong. In his 7th year he contracted peritonitis, which was cured in 2 months; had beri-beri in his 20th year and ever since has been suffering from cerebral neurasthenia; 6 years ago a diagnosis of tuberculosis of the apex was made, although he had no cough or expectoration; the following year climatic and tuberculin treatment were tried; he says he is susceptible to colds; at present little expectoration. Appetite normal; stools once daily.

Diagnosis.—Pulmonary tuberculosis in the second stage.

Present Illness.—Both constitution and nourishment poor; skin and subcutaneous tissue anemic; larynx somewhat reddened; neck long; no swelling of the jugular lymphatic glands; thorax flat; the region of the manubrium sterni sunken; breathing weak on both sides; in the upper lobes of both lungs a very weak respiratory sound is present; at the right apex there is a bronchial sound; no change is perceptible by percussion; normal precordial dullness; no anemic sounds; bowels sunken, but no change is perceptible. Von Pirquet reaction, +, +, +. Tubercle bacilli in the sputum can only be demonstrated by the use of anti-formin. Weight 42.8 kilos. Temperature 36.8°C.

Progress.—The first injection of 16 mg. was given on Jan. 19, 1915. On Jan. 20 the right apex had a short sound on both sides down to the third rib, where many râles were heard. Cough and expectoration present. The bacilli in the
sputum correspond to Gaffky's No. II. The second injection of 16 mg., the third of 17 mg., and the fourth of 17 mg., were given on Feb. 2 and 16, and Mar. 2, respectively; bronchial respiratory sounds at the right apex and a few râles at the left scapular region appeared on May 7, when the fifth injection of 16 mg. was given. On May 20 the body weight was 44.5 kilos. The râles had all disappeared; only the coarse respiratory sound of the right apex remained. The injection was, therefore, suspended.

The results of five sputum examinations were negative.

Case 8.—Y. I., male, aged 36 years. Father died of stomach trouble at 59 years of age; and mother died of pneumonia in her 56th year. Has six brothers and sisters, all of whom are healthy; wife and five children living; one child died immediately after birth. No inherited tendency toward tuberculosis could be established.

He has always been healthy; suffered from enteric catarrh in his 18th year; and from typhoid fever in his 28th. In Apr., 1914, contracted laryngeal tuberculosis; in August had fever, cough, and expectoration; a tender tumor as large as the tip of the little finger appeared at the anal region; it was operated on and is still excreting pus; since then all the symptoms have been worse; emaciation setting in; night sweats slight; appetite impaired.

Diagnosis.—Pulmonary tuberculosis in the second stage; left axillary lymphatic tuberculosis and tubercular ulceration at the anal region.

Present Illness.—Constitution poor; nourishment impaired; skin yellowish brown and somewhat anemic; conjunctiva anemic; larynx slightly congested; neck short and no swelling in the lymphatic glands; thorax symmetrical; breathing symmetrical; in both lungs dullness up and down the borders of the scapula; many râles were heard down to the second intercostal space; back of the left lung general prolongation of exhalation; swelling of the lymphatic glands of the left side; the left axillary glands were swollen to about the size of a pigeon's egg; tender, but no adhesions; normal precardial dullness; bowels normal; ulceration as large as a pea at the anal region; the edges show gradual transition, but no new growth of the mucous membrane; pus is present. The bacilli in the sputum correspond to Gaffky's No. VI. Von Pirquet reaction, +, +, -. Weight 46.5 kilos. Urine free from albumin and casts.

Progress.—The first injection of 15 mg. was given on Jan. 16, 1915. Severe sweats occurred that night, but subsided in 2 days; on Jan. 24 no râles were heard; on Jan. 29 the second injection of 16 mg. was given. That night a slight pain was felt at the left axillary glands; by massaging the region the swelling disappeared; the excretion of pus from the anal lesion ceased; a slight increase of expectoration was noted; the third injection of 16 mg. was given on Feb. 12, and fever subsided completely. All the clinical symptoms had gone except the short percussion sound at the left apex. The temperature and the results of bacteriological examination of the sputum are shown in the chart. Since then the sputum was examined several times under the microscope, but negative results were obtained. Weight 48.3 kilos.
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Case 9.—A. Y., female, aged 26 years. Father died of consumption; mother still living. One paternal uncle died of apoplexy; maternal uncles and aunts are all healthy; has three brothers and sisters, all of whom are healthy. Husband and two children also healthy.

The patient has been healthy since birth until Apr., 1914, when she had a hemorrhage; since then she has had five hemorrhages; case diagnosed as pulmonary tuberculosis; receiving climatic and medical treatment; appetite impaired; occasionally diarrheal stools two or three times daily, which, however, soon subsided.

Diagnosis.—Pulmonary tuberculosis in the third stage; right tubercular pleurisy.

Present Illness.—Constitution poor; nourishment impaired; skin and mucous membrane anemic; cheeks flushed; larynx slightly congested; neck long; no lymphatic glands swollen; typical pigeon chest; right lung very weak in respiratory sounds; slight dullness of frontal side of the right lung down to the fourth intercostal space; râles at apex; bronchial respiration elsewhere; slight dullness over lateral side of the right lung; râles and friction sounds also heard; few râles on lateral side of left lung at intercostal space; normal precordial dullness; no tenderness or hard nodules in the bowels. Body temperature 38.1°C. Pulse over 101. Body weight 43.7 kilos. The bacilli in the sputum correspond to Gaffky's No. VI.

Progress.—The first injection of 16 mg. was given on Feb. 9, 1915. On Feb. 14 the temperature fell to 37.6°C., when the patient was discharged from the hospital. In the evening the temperature rose to 38.2°C. The third injection (16 mg.) and the fourth (14 mg.) were given on Mar. 9 and Apr. 27, respectively, but brought about gradual rise of temperature, more bacilli in the sputum, and extension of the lesions, as shown in the chart. Emaciation gradually set in, and the body weight fell to 38.2 kilos. The injection of the preparation was therefore suspended for the time being.

Case 10.—E. T., male, aged 34 years. Father died of an indefinite disease; mother healthy. Six brothers and sisters, one of whom died while young, also of an indefinite disease. No inherited tendency toward tuberculosis.

The patient had been healthy until he was about 14 years old, when he contracted pleurisy after a cold, and then tuberculosis. The symptoms were becoming worse. In 1914 he was operated on for hemorrhoids. Since then he has been suffering from an increase of cough, expectoration, and fever; at the same time night sweats and dyspnea appeared; could not walk because of emaciation. Appetite poor.

Diagnosis.—Pulmonary tuberculosis in the third stage, and hemorrhoids.

Present Illness.—Constitution robust; nourishment impaired; skin and mucous membrane very anemic; features agonal; larynx somewhat congested; neck long; no swollen lymphatic glands; thorax flat; on the left side breathing impaired; dullness down to the second rib on the frontal side of the right lung; on the same side slight dullness down to the costal margin; all the remainder dull; at the region
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where slight dullness is elicited bronchial sounds are heard on auscultation; no respiratory sounds in the region of the dullness; slight dullness down to the fifth intercostal space on the frontal side of the left lung; at the second intercostal space tympanic sounds at some points; on the lateral side dullness over a region as wide as three fingers; bronchial respiratory sounds are heard over these regions; normal precardial dullness; no change in the heart sound. Von Pirquet reaction, +, +, +. The bacilli in the sputum correspond to Gaffky's No. III. Temperature 38.9°C. Pulse 108, weak. Weight 50.1 kilos.

Progress.—The first injection of 16 mg. was given on Jan. 19, 1915, the second (16 mg.) on Feb. 2. Temperature fell to 37.3-37.7°C. on Feb. 9. The third injection (16 mg.) was given on Feb. 16. By this time the general condition improved markedly. The fourth injection (17 mg.) was given on Mar. 2. The temperature rose to 38°C. and the bacilli in the sputum also increased to Gaffky's No. VII. The physical phenomena were intensified until an interval of 3 weeks had elapsed, when the temperature fell to 37.1°C. The fifth (16 mg.), the seventh (15 mg.), and the eighth injections (16 mg.) were given on Apr. 7 and 20, and May 4, respectively. At present the temperature is about 37°C. The physical phenomena are represented in the accompanying charts. Though improvement is obvious, the bacilli in the sputum have not disappeared.

Case 11.—N. T., male, aged 23 years. Father living; mother died of typhoid fever; seven paternal uncles and aunts, three of whom died of an indefinite disease; one is suffering from tuberculosis; all the rest are healthy; no brothers or sisters. The patient has been weak since birth; contracted whooping cough in his 8th year; ever since has been unwell during the winter; contracted pneumonia once; has empyema of the maxillary sinus; contracted apical tuberculosis 3 years ago, which subsided after clinical treatment, but is not yet completely cured; rarely has pain in the thorax; appetite good; stools once daily.

Diagnosis.—Pulmonary tuberculosis in the first stage.

Progress.—The first injection of 16 mg. was given on Dec. 11, 1914. Many râles appeared along the line bordering the right lung and the liver, as is shown in the chart; the apex showed slight dullness with a few râles; many râles were heard about the region corresponding to the heart; on the lateral side of the right lung slight dullness was produced over a region as wide as three fingers, where some râles were also heard. Tubercle bacilli in the sputum correspond to Gaffky's No. II. These phenomena completely disappeared in 7 days. The second injection (16 mg.), the third (16 mg.), and the fourth (16 mg.) were given
on Dec. 26, Jan. 8, and 22, respectively. No reaction was produced, and the results of the fifth injection (17 mg.) brought about some reaction. Since then four injections were made, but no reaction was produced. All examinations of the sputum have been negative. Von Pirquet negative. Treatment suspended.

SUMMARY.

A general review of the cases will, I think, indicate that the preparation greatly improves or apparently cures pulmonary and surgical tuberculosis in the first and second stages, and that it seems also to produce beneficial effects upon the disease in the third stage. The duration of these beneficial effects is still to be established by more numerous trials and many years of observation.

The preparation must be given intravenously, and the doses must be increased or decreased according to the age and constitution of each patient (page 156). Moreover, it should be borne in mind that the pathological phenomena and the constitution of each patient have much to do with the determination of the dose. The manner of action of the preparation is not yet entirely clear. But if it acts primarily upon the tissues which bear the tubercular lesions and then indirectly against the germ, as I assume at present, the activity which the tissues exert will have much to do with the efficacy of the preparation. If this hypothesis is correct, the minimum doses (10 to 12 mg.) will be best suited to a patient who is greatly emaciated, and should be gradually increased as the reactions, pathological processes, nutrition, etc., indicate. In any case, the dose of the preparation must be determined by the condition and constitution of the patient. In animal experiments I have been fortunate enough to obtain results which no other preparation has given. The clinical application and the establishment of its full efficacy in human cases must be left to the physician.

I wish to express my indebtedness to Drs. Kitasato, Shiga, and Kusama, and also to Dr. Kanai and other members of the Kitasato Institute.

2 The preparation has since been named "cyanocuprol."
The Roman numerals in Text-figs. 1 to 6 refer to the numbers in Gaffky's table:

I. Only 1 to 4 bacilli in whole preparation.
II. Only 1 on an average in many fields.
III. Only 1 " " " " each field.
IV. 2 to 3 " " " " " "
V. 4 to 6 " " " " " "
VI. 7 to 12 " " " " " "
VII. 13 to 25 " " " " " "
VIII. About 50 " " " " " "
IX. About 100 " " " " " "
X. Over 100 in each field.

**TEXT-FIG. 1. Case 2, male.**
The sputum is free from bacilli at present.

**TEXT-FIG. 2. Case 3, male.**
The patient did not report again and therefore received no further treatment.
TEXT-FIG. 3. Case 5, male. The sputum was examined under the microscope; negative results were obtained each time.

TEXT-FIG. 4. Case 8, male. Every microscopic examination has been negative for more than 4 months.
TEXT-Fig. 5. Case 9, female. The symptoms became worse and the number of bacilli in the sputum increased.

TEXT-Fig. 6. Case 10, male. After 4 months' treatment the sputum was free from bacilli.
Text-Fig. 7. Temperature curve. Case 1, female.

Text-Fig. 8. Temperature curve. Case 3, male.
Text-Fig. 9. Temperature curve. Case 8, male.

Text-Fig. 10. Temperature curve. Case 4, female.
TEXT-Fig. 11. Temperature curve. Case 9, female.
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Text-Fig. 15. Case 6, male. Nov. 26, 1914.
TEXT-Fig. 16. Case 6, male. Dec. 8, 1914.
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Text-Fig. 17. Case 6, male. Jan. 12, 1915, no symptoms.
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Text-Fig. 18. Case 7, male. Feb. 16, 1915.
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Text-Fig. 20. Case 7, male. Feb. 26, 1915.
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Text-fig. 21. Case 7, male. May 7, 1915. Note the appearance of rales in the intrascapular region, after an interval of 3 months during which time he did not receive the injection.
Text-Fig. 22. Case 7, male. May 20, 1915. The râles disappeared after one injection of 15 mg. and the injection was discontinued.
Text Fig. 23. Case 9, female. Feb. 8, 1915.
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Text-Fig. 26. Case 10, male. Jan. 19, 1915.
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Bronchial respiration sound.

Weak " "

Loss of " "

Rough " "

Interrupted " "

Long " "

Coarse riles.

Fine "

Consonant riles.

Vesicular "

Friction "

Sibilant "

Crackling "

Sonorous "

Short sound.

Dull "

Metallic "

Heart "

Text-Fig. 27. Case 10, male. Feb. 13, 1915.
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Text-Fig. 29. Case 10, male. May 17, 1915.
Text-Fig. 30. Case 11, male. Dec. 3, 1915.
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Text-Fig. 31. Case 11, male. Dec. 11, 1915.