NERVOUS COMPLICATIONS FOLLOWING TREATMENT BY GOLD SALTS

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Complications affecting the nervous system following treatment by gold salts are very uncommon. I can find no reference to their occurrence in the British or American literature, with the exception of a warning by Findlay¹ and Copeman² that neuritis may occur, but no further details are given. Hartfall and Garland,^{3,4} in a recent analysis of 400 cases treated by gold salts, have found various complications in 37 per cent. of their cases, but none affecting the nervous system. French authors, however, have reported a few such cases. Nervous complications can occur soon after the first injection of the salt, or more commonly near the end of the first or even of subsequent courses. They are often preceded by other signs of susceptibility, especially of the skin, such as erythematous rashes, or even, though rarely, exfoliative dermatitis.

Survey of the Reported Cases

Chavany and Chaignot⁵ have described a syndrome the main signs of which are: (a) a burning, stabbing pain of great severity, which is generalized and not confined to any particular nerve tract, with cutaneous hyperaesthesia, and often accompanied by fever (*grippe aurique*), with a minimum of objective physical signs; (b) great mental agitation, depression, and fear, with a constant desire to walk about, especially at night and in the early hours of the morning; (c) insomnia, which is very resistant to treatment; (d) excessive sweating; (e) great fatigue; (f) marked loss of flesh; (g) occasionally irregular fibrillary twitchings of the muscles of the trunk and limbs.

These authors have described two cases. One was that of a man suffering from pulmonary tuberculosis, who after having received a total amount of 3.5 grams of gold salt, suddenly complained of violent pains in the legs, together with intractable insomnia. So great was the mental agitation and restlessness that he had to be sent to an asylum. Generalized fibrillary twitching affected the whole body, with the exception of the tongue and facial muscles. After three months improvement commenced, and he made a good recovery. Similar cases have been reported by Gernez,⁶ Gougerot,⁷ Jacob,⁸ de Cires,⁹ Lebeuf,¹⁰ Alajouanine,¹¹ and Bernard and Morin.¹² All made good recoveries. Devic and Bouquin¹³ have described two similar cases in which the insomnia returned after resuming the injections. Hinault and Mollard¹⁴ have quoted two cases; one tried to commit suicide on the evening after the third injection of thio-crisine. The other developed mental troubles, for which he had to be confined to an asylum for three months. These authors, however, are by no means convinced that the gold salts were entirely responsible for these abnormal mental states.

The peripheral nerves may be the structures chiefly involved. Roger¹⁵ has reported the case of a consumptive patient who had received 7.25 grams of crisalbine during six months. Five months later weakness and pain on pressure over the calves were found, with objective loss of sensation over the lower third of both legs and disappearance of the ankle-jerks. Farjon¹⁶ has described a case with severe sciatica and weakness of the muscles supplied by both sciatic nerves, which developed during a course of crisalbine. The pain returned after a later injection. Similar cases have been recorded by Alajouanine,¹¹ Beyerholm,¹⁷ and Chavany and Boudillon.¹⁸

Mollard¹⁹ has reported three cases of peripheral neuritis following injections of gold. The first developed a paresis of the right brachial plexus during the third course of injections of gold salts; it cleared up after a month. Another was a man with a flaccid paralysis of the muscles of the left upper and lower limbs which occurred suddenly, recovery ensuing in forty-eight hours. The third suffered from a bulbar palsy, with paralysis of the right facial nerve of the lower motor neurone type. The case described by Tzanck²⁰ was that of a woman who suffered from loss of power in the right limb; recovery took place in two months' time. Lambea's patient²¹ developed a double muscular spinal palsy. Fledelius²² has recorded the case of a patient who suffered from pain and paresis of the left upper and lower limbs, with disappearance of the reflexes. The cerebro-spinal fluid contained an increase of lymphocytes and protein. All had received treatment with gold salts, and all made good recoveries. Moulouguet and Perron's patient,²³ after a series of injections of synocrisin, developed a bilateral abductor paralysis of the vocal cords for which a tracheotomy was necessary. Cases of facial neuralgia, with trouble in accommodation and transitory blindness, have been reported by Hinault and Mollard.¹⁴

Motor involvement of Landry's type may be the outstanding feature. Roger¹⁵ has reported a patient with phthisis who, after receiving several courses of crisalbine without any ill effect, suddenly complained of acute headache and pain in the limbs, with fever. Three days later his right leg became weak, followed by a similar condition in the left, together with difficulty in micturition. A little later he complained of a feeling of heaviness and weakness in both upper limbs. Partial flaccid paralysis of both lower limbs, with absent knee- and ankle-jerks, was found. There was weakness of both upper limbs. Sensation was diminished up to the nipple level. The cerebro-spinal fluid showed an increase of cells and albumin, with diminution of the sugar. The paralysis progressed for a time, and then slow improvement commenced. These authors also report another similar case. In Bourgeois's patient²⁴ flaccid paraplegia started, followed by paralysis of the right upper limb. A week later bulbar palsy developed, from which he died.

Epileptiform convulsions have occurred during treatment with gold salts. Roger¹⁵ has reported the case of a patient who, when 8 years of age, was trephined on account of an injury to the head. No further complications occurred. When 21 years old he was treated for phthisis with gold salts. A month after the last injection he suddenly complained of pain in the scar on his head and tingling in the left forearm. During the next week he had several generalized and local epileptiform convulsions, limited to the right upper limb, with some temporary weakness. After a week, however, the attacks ceased. The authors discuss the differential diagnosis, and conclude that the scar from the operation prepared the ground for the abnormal action of the gold. They quote a case described by de Cambo who suffered from epileptiform convulsions after each injection of gold salts. These disappeared on discontinuing the drug. Radovici's patient²⁵ developed a facial tic, with blepharospasm after similar injections. Cases of extension from an active tuberculous focus to the meninges after treatment with gold salts, with fatal results, have been reported by Berthier²⁶ and Lebeuf and Mollard.²⁷

That gold can penetrate into the tissues of the central nervous system is proved, since it has been found in the cerebro-spinal fluid in two out of three patients treated with gold salts by Lebeuf, Mollard, and Pauget,²⁸ and also in another case reported by Gernez.⁶ Further, Steiner and Fischl²⁹ have found traces of gold in the brains of dogs after injections of solganal and in relatively

large quantities in the grey matter of a patient who died from disseminated sclerosis, and who had been treated with injections of gold.

Polynuritis following Treatment by Gold Salts

A woman aged 42 was admitted to the Derbyshire Royal Infirmary on June 18th, 1936, complaining of weakness and a feeling of pins-and-needles in all four limbs. Until 1927 her health had been good, but since then she had begun to suffer from pain and swelling in the ankles, wrists, and finger-joints of a rheumatic nature. During March, 1936, a course of myocrisin was started by weekly intramuscular injections of 0.01, 0.05, 0.1, 0.2, 0.3, 0.3, 0.3, 0.3 grams. The rheumatism improved. Four days after the last injection, however, she began to stagger on walking, and complained of weakness, a sensation of pins-and-needles in her legs, and a feeling as though they were "bound round with strips of plaster." These symptoms commenced first in her feet; they then spread to her legs and arms, and later to the forearms and hands. She never complained of pain at any time. There was no history of any recent infection.

On examination she was found to be a woman of moderate physique. Her appetite was good, and her diet had been well balanced and plentiful. There was no history of alcoholic excess. Her weight was 5 st. 10 lb. She was not anaemic. The tongue, though not sore, was red and glazed, nearly the whole of the surface being devoid of papillae. All her teeth were false. She was mentally clear, and co-operated well throughout the examination. The speech was indistinct, and she spoke in a nasal tone. The facial folds were less marked than usual, and the forehead was devoid of wrinkles; both sides of her face showed some flattening, with lack of mobility on voluntary movements, which gave her a fixed, expressionless look, but there was no asymmetry. She could close her eyes, but not so firmly as a normal person, and she could blow out her cheeks, though imperfectly. The left palpebral fissure was rather smaller than the right. There was no difficulty in swallowing, and the soft palate moved well. The pupils reacted normally. There was no ophthalmoplegia or nystagmus. The fundi showed nothing abnormal. Smell, sight, and hearing were unimpaired.

There was marked swaying on standing, and incoordination of the hands and feet. There was no stiffness of the neck. Marked generalized symmetrical weakness of the upper and lower limbs was found, the muscles being toneless and flabby, but there was no appreciable wasting. No muscle was completely paralysed, there being movement at every joint, though these were of small range and feeble, especially at the wrists and ankles, where the extensor muscles were weaker than the flexor. No pain was caused on grasping the muscles, nor on deep pressure over the nerve trunks, which were not felt to be thickened. There were no fibrillary twitchings. The reflexes of the upper and lower extremities and of the abdomen were absent. The plantar reflexes were flexor.

Objective sensation was nowhere absolutely lost, but there was marked impairment to pin pricks, to differences of heat and cold over the fingers and toes, and to cotton-wool from the middle of the forearms and the lower portion of the thighs downwards. Sense of position and vibration were diminished below the knees and in the hands. There were no vasomotor or trophic disturbances, nor any interference in the functioning of the bladder or rectum. Nothing abnormal was found in the cardiovascular, respiratory, or genito-urinary systems. There was nothing pointing to disease of the alimentary system. The liver, spleen, and lymphatic glands were not enlarged. There was no disease of the skin or any sign of focal sepsis. The wrist, finger, and ankle-joints showed evidence of non-active rheumatic disease. At no time was there found any rise in the temperature or in the pulse rate.

The following investigations were made. Haemoglobin 90 per cent.; red blood cells, 4,560,000 per c.mm.; white blood cells, 8,000 per c.mm., with a normal differential count. The red cells were normal in shape and size. The Wassermann and Kahn reactions were negative. No albumin or casts were found in the urine. The cerebro-spinal fluid was colourless and under normal pressure. There were six lymphocytes per c.mm., and the protein was raised to 80 mg. per cent., with a normal sugar and chloride content. Gastric analysis showed the absence of free hydrochloric acid, even after an injection

of 0.5 mg. of histamine. The response of the muscles of the upper and lower extremities to faradism and galvanism showed no reaction of degeneration.

The patient was given a generous mixed diet, rich in vitamins, especially vitamin B, with acid. hydrochlor. before food. The limbs were suitably splinted. Massage, active and passive movements, and later re-educational exercises were ordered. A course of injections of sodium thiosulphate was given intravenously.

Improvement was satisfactory. In a few days she was able to feed herself, and the sensations of tingling and of pins-and-needles began to subside. A little later her limbs became stronger, and by the end of the eighth week she was starting to walk again.

Four months later she could walk fairly well, though a little unsteadily. Muscular power was stronger. The facial muscles were still a little weak. The reflexes had all returned, except the right ankle-jerk. She had lost all the subjective and objective signs of sensory disturbance, except that the sense of position of the toes and of vibration over the legs and feet were still impaired, though to a less extent than formerly.

Prognosis and Treatment

The prognosis of the nervous complications which may follow treatment by gold salts is favourable, although some reservation must be made for those suffering from mental disturbance. Since in all the cases discussed the amount of gold salts used has not approached the average toxic dose, and the injections have been suitably spaced, it must be assumed that these patients' nervous systems were more susceptible; it may be safer to adopt the smaller dose and larger interval between the courses as recommended by Hartfall and Garland^{3,4}—that is, weekly injections of gold salt, ranging from 0.05 to 0.1 gram, until a total of 1 gram has been given, and then to interpose an interval of at least twelve weeks before starting another course.

Mollard¹⁹ and others have advised that the gold salts should be suspended in oil and given intramuscularly, because absorption will be slower and there should thus be less risk of any accident occurring. Hartfall and Garland,^{3,4} however, from the analysis of their cases, are of opinion that there is no more risk with aqueous solutions, even if given intravenously. Several writers have recommended dissolving the gold salts in a solution of calcium gluconate to minimize the risk of any complication following. Crosby²⁰ gives calcium gluconate and liver extract by the mouth throughout the treatment, and, in all cases of severe reaction, intravenous injections of sodium thiosulphate, and vitamins A and D, but he and others are not enthusiastic about this. Hartfall and Garland^{3,4} do not think calcium prevents any toxic symptoms. Slot²¹ has emphasized the importance of small doses and suitable intervals. He finds colloidal sulphur in drachm doses at night a useful adjuvant. Strzykowski²² recommends, as an antidote against the poisonous effects of the heavy metals, giving by mouth 50 c.cm. of a solution of hydrogen sulphide prepared according to his method. If there is any sign of deficiency, a diet rich in vitamins, together with some preparation containing vitamin B, should be given. Iron in large doses and hydrochloric acid should be ordered for suitable cases.

Discussion

Although the nervous complications following treatment by gold salts are rare, their possible occurrence might have been foretold, because of the relationship of gold to the other metals such as lead, arsenic, bismuth, silver, and mercury. In complex cases, however, all possibilities must be examined, since there may be other factors present to produce such a condition as polynuritis. In the previously described case it may be contended that the patient might have developed this nervous disease

independently of the treatment by gold salts. Sporadic cases of polyneuritis with facial diplegia of the so-called "acute infective type," though uncommon, do occur.

Douthwaite,³³ under the title of "gastrogenous polyneuritis," has grouped together a series of cases of peripheral neuritis unrelated to any obvious causal agent, but in each of which there is some associated disease of the stomach. Case 4 of his series, a woman with polyneuritis and achlorhydria, is somewhat similar to the one described in this paper, except that there was a slight anaemia present in his case. Douthwaite's view is that the health of the peripheral nerves may be dependent on an adequate supply of some essential factor, which may fail in cases of achlorhydria following a chronic gastritis.

Summary

1. The occurrence of nervous complications is the rarest of all known accidents following treatment by gold salts.
2. A survey of the reported cases, mainly from the French literature, has been made.
3. A case is reported of a woman who suffered from a four-limbed peripheral neuritis, accompanied by bilateral facial weakness and slight bulbar involvement, occurring at the end of a course of treatment with gold salts.
4. The differential diagnosis, prognosis, and treatment are discussed.

REFERENCES

- ¹ Findlay, G. W. M.: *Recent Advances in Chemotherapy*, 1930, p. 469.
- ² Copeman, W. S. C.: *Treatment of Rheumatism in General Practice*, 1935, p. 48.
- ³ Hartfall, S. J., and Garland, H. G.: *Lancet*, 1935, ii, 8.
- ⁴ Idem: *Ibid.*, 1936, i, 1459.
- ⁵ Chavany, J. A., and Chaignot, A.: *Presse Méd.*, 1934, xlii, 478.
- ⁶ Gernez, C.: *Rev. de la Tuberculose*, 1935, i, 386.
- ⁷ Gougerot, M. H.: *Bull. Soc. Franç. de Derm. et de Syph.*, 1931, xxxviii, 53.
- ⁸ Jacob, P.: *Bull. et Mém. Soc. Méd. des Hôp. de Paris*, 1934, i, 280.
- ⁹ de Cires, E.: *Semana Médica*, 1933, xl, 1969.
- ¹⁰ Lebeuf, F., Pétauud, C., and Mollard, H.: *Bull. Soc. Franç. de Derm. et de Syph.*, 1931, xxxviii, 142.
- ¹¹ Alajouanine, T., Mauric, G., and Fauvert, R.: *Bull. et Mém. Soc. Méd. des Hôp. de Paris*, 1934, i, 128.
- ¹² Bernard, E., and Morin, M.: *Ibid.*, 1936, lii, 469.
- ¹³ Devic, A., and Bouquin, P.: *Lyon Méd.*, 1935, clvi, 406.
- ¹⁴ Hinault, V., and Mollard, H.: *Traitement Aurique de la Tuberculose*, 1934.
- ¹⁵ Roger, H., Alliez, J., and Jouve, A.: *Arch. de Méd. Gen. et Col.*, 1935, iv, 145.
- ¹⁶ Farjon, A., Maizilly, P., and Lefèvre, P.: *Presse Méd.*, 1928, xxxvi, 1218.
- ¹⁷ Beyerholm, O.: *Hospitaltidende*, 1926, xxxvi, 881.
- ¹⁸ Chavany, J. A., and Boudillon, E.: *Rev. Neurol.*, 1933, ii, 628.
- ¹⁹ Mollard, H.: *Journ. Méd. Franç.*, 1935, xxiv, 4.
- ²⁰ Tanck, A., Pautrat, J., and Klotz, H. P.: *Bull. et Mém. Soc. Méd. des Hôp. de Paris*, 1934, i, 432.
- ²¹ Lambea, J.: *Arch. de Méd. Gen. et Col.*, 1935, iv, 145; *Abstr. Méd. Iberia*, xx, No. 440, 421.
- ²² Fledelius, M.: *L'encephale*, 1934, xxix, 620.
- ²³ Moulouguet and Perrer: *Arch. de Méd. Gen. et Col.*, 1935, iv, 158; *Abstr. Soc. Laryngol. de Hôp. de Paris*, January 18th, 1928.
- ²⁴ Bourgeois, P., Thiel, H., and Broutman, J.: *Bull. et Mém. Soc. Méd. des Hôp. de Paris*, 1935, li, 90.
- ²⁵ Radovici, A., Sphachter, M., and Popovici, A.: *Paris Méd.*, 1934, ii, 376.
- ²⁶ Berthier, J., Rouet, and Offant: *Arch. de Méd. Gen. et Col.*, 1935, iv, 147; *Abstr. Soc. de Méd. de Marseille*, June 27th, 1932.
- ²⁷ Lebeuf, F., and Mollard, H.: *Bull. Soc. Franç. de Derm. et de Syph.*, 1932, xxxix, 1594.
- ²⁸ Lebeuf, F., Mollard, H., and Pauget, P.: *Ibid.*, 1931, xxxviii, 513.
- ²⁹ Steiner, G., and Fischl, V.: *Klin. Woch.*, Berlin, 1929, viii, 582.
- ³⁰ Crosby, G. J. V.: *Lancet*, 1936, i, 1463.
- ³¹ Slot, G.: *Ibid.*, 1936, i, 157.
- ³² Strzyzowski, C.: *Presse Méd.*, 1936, xlv, 780.
- ³³ Douthwaite, A. H.: *British Medical Journal*, 1936, ii, 525.

According to the Budapest correspondent of the *Journal of the American Medical Association* there are 3,697 doctors in that city or one doctor to 370 persons; 291 are women, sixty-one are above 70 years of age, and most between 30 and 35; 1,561 are Christians and 1,137 Jews; 39 per cent. are unmarried. Four-fifths are specialists and only one-fifth general practitioners; 33 per cent. have no telephone, and 17 per cent. do not subscribe to any medical journal.

INTESTINAL TUBERCULOSIS LIMITED TO THE APPENDIX

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The frequent involvement of the appendix in intestinal tuberculosis has long been recognized, being estimated as occurring in about 70 per cent. of the cases (Engelsmann, 1918; Winkler, 1910; Schwatt and Steinbach, 1923). Fenwick and Dodwell (1892), who examined the reports of 2,000 necropsies at the Brompton Hospital, came to the conclusion that it is quite an exception to find the appendix free from disease when there is tuberculous ulceration of the ileo-caecal region. It is also well known that tuberculosis of the appendix rarely shows clinical signs; this has been attributed to simultaneous involvement of the ileo-caecal region and of the appendix, wherein the symptoms of the former conceal those of the latter. On the other hand, owing no doubt to the scarcity of material, it is still uncertain whether the appendix is ever the first or only part of the intestine to be attacked by tuberculosis. (Naturally I am not referring to cases in which the appendix is the site of the primary tuberculous focus—primary complex, that is, the place of entry for the first infection of the whole organism (Woerner 1911, Miloslavich 1912)—but to cases of so-called secondary intestinal tuberculosis resulting from tuberculosis already established in another organ, generally the lungs.)

When tuberculosis of the appendix is discovered post mortem tuberculous lesions are also observed elsewhere in the intestines. Discovery of tuberculosis in excised appendices in only exceptional cases permits conclusions as to the site of the primary intestinal lesions. In 515 cases of appendicitis Noehren established microscopically the existence of tuberculous lesions in 3 per cent.; Mueller in 1.6 per cent.; Miloslavich (1912) in about 1 per cent.; Deaver (1905) in 0.27 per cent.; Drissen and Zollinger (1935) in 0.3 per cent. See also Nové-Josserand, Roulet, and Bertrand (1933).

Present Investigation

The present contribution to the question of the primary or exclusive localization of intestinal tuberculosis in the appendix is based on material from eighty-four necropsies on tuberculous subjects; in fifty of these careful histological examination was carried out.* The cases were divided into six groups, in which the following figures were obtained:

1. Absence of tuberculosis of the intestine and appendix was established in thirty cases, a number corresponding to the frequency of secondary intestinal tuberculosis maintained by Orth (1887), Zahn (1902), M. J. Stewart (1928), E. H. Rubin (1930), but less than that obtained by Engelsmann (1918) and Kaufmann.
2. Intestinal tuberculosis without involvement of the appendix was observed in twenty-nine cases.
3. Six cases showed mild intestinal tuberculosis with involvement of the appendix.
4. Advanced tuberculosis of both intestine and appendix occurred in eleven cases.
5. Advanced tuberculosis of the appendix with slight or incipient changes in the intestine was observed in five cases.
6. The appendix was the only diseased section of the intestine in three cases.

* Owing to the recent death of Dr. E. Weichherz, a statistical inquiry into the question at issue, which was being made by him at the Bulovka Hospital, Prague, has unfortunately not been completed.