more accurate observations on this type of case. In the case of multiple secondary cysts, too, the surgeon is often faced with an apparently insoluble problem, and it is possible that we may have to wait for the discovery of some method of general intravenous therapy before we achieve complete success in their management.

Conclusion

In conclusion, I would urge that, although we have learnt a great deal about the disease, although we probably know as much about its behaviour, its clinical manifestations, and its treatment as any other disease we meet with, it would be wrong for us to become complacent and not to continue making observations and experimenting to still further elucidate problems which, although they may appear somewhat academic, may become in reality of great practical importance. In this country of Australia we all have unrivalled opportunities to investigate this disease, both in man and in animals, and it is our duty to contribute our share to future advances in its study.

AGRANULOCYTOSIS WITH PURPURA HAEMORRHAGICA FOLLOWING GOLD THERAPY

WITH A NOTE ON PREVENTION OF COMPLICATIONS

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The value of gold salts as a therapeutic measure in infective diseases such as pulmonary tuberculosis and rheumatoid arthritis is now well recognized. Complications arising from its employment are, as a rule, of a comparatively mild nature. In the course of a large experience of its use in pulmonary tuberculosis, and also of a smaller experience in rheumatoid arthritis, we have observed only one serious and fatal case, which we feel justified in reporting in view of several cases of agranulocytosis which have recently been recorded in the English literature.

Emile-Weil and Bousser,⁸ in their review of the blood dyscrasias due to gold which had appeared in the literature up to 1932, found thirty cases in all. As such a large number of cases have been treated with gold since its inception they consider that the percentage of these accidents must be very small. On the other hand, Hartfall and Garland,¹⁴ in a series of 100 cases of rheumatoid arthritis treated with crisalbine, had three deaths. One was due to agranulocytosis, and the other two to purpura haemorrhagica.

Case Record

The following is the history of a case of agranulocytosis with purpura haemorrhagica which came under our care.

History.—The patient, a woman aged 61, had suffered from rheumatoid arthritis of an advanced degree for nineteen years. The fingers, elbows, ankles, knees, sterno-clavicular, and jaw joints were all involved in the arthritic process. There was partial ankylosis of the knee- and elbow-joints. X-ray of the knees showed extensive arthritic change of the

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rheumatoid type in both joints. The blood sedimentation rate was 24 mm. in the first hour by the Westergren method.

Treatment.—The patient was given solganol B oleosum intramuscularly in weekly doses of 0.01, 0.05, 0.1, and 0.2 gram, the latter dosage being continued until 2.5 grams had been given. The joint condition had now shown marked improvement, and the sedimentation rate was down to 9 mm. After four weeks' rest a second course was started. It was only after the fifth injection of the second course that a faint erythematous rash was observed. The sedimentation rate had by this time risen to 16 mm., and the leucocyte count, which had hitherto been normal, was found to be 3,100 per c.mm. The differential white cell count (Dr. Eidinow) was: polymorphonuclears, 27 per cent.; lymphocytes, 69 per cent.; hyaline cells, 2 per cent.; eosinophils, 1 per cent.; myelocytes, 1 per cent.

A week later an extensive purpuric eruption appeared on the trunk, limbs, and buccal mucous membrane. There was a large haemorrhagic bulla on the sole of one foot, and the patient had epistaxis and slight haemoptysis. The temperature was now 100.6° F. She had previously been afebrile. The liver and spleen were not enlarged. The bleeding time was ten minutes. The leucocyte count was now 1,100 per c.mm., and the differential count was: polymorphs, 10 per cent.; lymphocytes, 87 per cent.; hyalines, 3 per cent.; eosinophils, 0 per cent. (Dr. Eidinow).

On admission to Battersea General Hospital under one of us (Ph. E.) the blood findings obtained by Dr. A. H. Haler were as follows: erythrocytes, 2,500,000; haemoglobin, 56 per cent.; colour index, 1.13; leucocytes, 800; polymorphs, 7 per cent.; hyalines, 1 per cent.; Türk cells, 1 per cent.; lymphocytes, 90 per cent.

There was some anisocytosis, slight poikilocytosis, no nucleated red cells, and no punctate basophilia; platelets were 70,000; mean cell diameter, 7.20 μ .

Progress.—Calcium gluconate and pentose nucleotide were administered, and a blood transfusion of 250 c.cm. given. Coagulen "ciba" was also given. Some definite improvement occurred after the blood transfusion, but late the same evening the patient died somewhat suddenly. A post-mortem examination was performed by Sir Bernard Spilsbury, to whom we are indebted for the report quoted below.

Post-mortem Report.—"External examination reveals oedema of the lumbar region and of the backs of the thighs. There are haemorrhages in the left conjunctiva, extensive into and above the upper lip, especially on the left side, and in the skin from the angles of the mouth down to the lower jaw. There are a few petechiae in the skin of the face, and others scattered over the front of the chest and abdomen, rather more on the arms, and numerous on the wrists and hands. There are a few on the thighs, more on the legs, very numerous on the feet, especially the left foot, close to the base of the toes. There is haemorrhage into the skin of the

whole of the right buttock, extending over the anterior abdominal wall. Internal examination shows the pericardial cavity obliterated by old and fine adhesions. Several small haemorrhages are present in the back of the ventricle, and a large area on the surface of the right auricle. The size of the heart and its cavities is normal. The heart muscle is pale, with numerous haemorrhages in the myocardium, and microscopically some brown atrophy. There is some old thickening of the mitral valve and slight atheroma of the lower end of the aorta. The coronary arteries are normal. The air passages are congested, and contain a little blood-stained mucus. Numerous large petechiae are present in the mucous membrane of the lower part of the larynx and trachea. Old pleural adhesions extend round the whole of the right lung and the greater part of the left. The lung shows general emphysema and some chronic bronchitis. The backs and the bases are congested. Old adhesions extend round the whole of the liver and spleen, and there are some pelvic adhesions, chiefly between the uterus and the rectum. The liver is pale: fine fatty degeneration of the liver cells has occurred in the centre of the lobules, microscopically. The spleen is normal. The kidneys are rather small, there being a slight arteriosclerotic change. The bladder shows numerous haemorrhages in the mucous membrane. Much urine is present, apparently free from blood. The suprarenals and pancreas are normal. The tongue is furred and bruised at the tip, the tonsils healthy, the stomach containing some bile-stained fluid but no food. Numerous haemorrhages are seen in the mucous membrane at the pyloric end, and large subserous haemorrhages at the cardiac end in front. The small intestine is stained red, but no disease is apparent, and there is no blood in the contents. Numerous small haemorrhages are present in the mucous membrane of the large intestine, becoming very numerous in the lower part. The uterus is drawn to the left by adhesions and is rather small in size. A tiny cervical polyp projects from the external os and another one in the lower part of the fundus. The ovaries are atrophied. A fair amount of subdural haemorrhage is seen round the occipital lobes, especially on the left side, and some round the left lobe of the cerebellum."

Complications of Gold Therapy

These may be divided up into effects on (1) the skin, (2) the mucous membrane, (3) the liver and kidneys, and (4) the haemopoietic system. We would emphasize that apart from a few cases of degenerative hepatitis gold accidents have only proved fatal when the haemopoietic system has been involved. Émile-Weil and Bousser divide the latter up into: purpura simplex, which is not fatal; purpura haemorrhagica, which is frequently fatal; isolated haemorrhages, which are not fatal; and agranulocytosis and aplastic anaemia, which nearly always cause death. A few cases of purpura combined with agranulocytosis (apart from the case here outlined) have been previously reported on the Continent. Angéras and Ginsbourg¹ record a fatal case in a girl of 19 suffering from pulmonary tuberculosis: she was commencing her second course of crisalbine; no eosinophilia was present. Another fatal case is reported by Achard, Coste, and Cahen²: the patient was a woman, aged 48, who had had 4.85 grams of solganol B in doses of 0.25 gram; death was stated to be due to meningeal haemorrhage.

As regards the causation of toxic manifestations, Émile-Weil and Bousser⁷ consider them due to a sensitivity to gold. Among four cases of purpura or haemorrhage in which they tried special intradermal and cutaneous tests with gold three were positive. In support of this view Hudson¹⁵ points out that many of the cases occurred soon after the commencement of the second course. Others have suggested that they may be due to rapid absorption of pathological products, possibly of the histamine or peptone type.^{4 11} They are certainly not due to poisoning by gold. Feldt¹⁰ points out that animals killed by large doses of gold do not develop these phenomena, but die of respiratory and vasomotor paralysis. Purpura combined with agranulocytosis has evidently a very serious prognosis, as all three cases so far reported have proved fatal. McCarthy and Wilson,¹⁷ who have reviewed the blood dyscrasias following arsphenamine injections,

find a mortality of 14 per cent. in purpura with agranulocytosis. They state that the prognosis depends on the extent to which the granulocytes are reduced.

The most effective treatment of agranulocytosis is blood transfusions repeated as often as is found necessary. Subcutaneous injections of blood have also been used, and adrenaline and liver by mouth.⁹ Intravenous glucose,¹⁵ hyposulphite of sodium or magnesium,⁸ and sodium nucleinate³ are also recommended.

Prevention of Complications

Before starting gold therapy the patient should always be questioned with regard to a personal or family history of purpura or bleeding. Gold salts should not be given to cases with such a history.⁸ They should likewise not be given following substances which affect the bone marrow, such as thorium.² Blood counts should be carried out frequently during the treatment (at least once a month) in order to detect an incipient agranulocytosis, aplastic anaemia, or thrombocytopenia. We cannot over-emphasize the necessity for this in the gold treatment of rheumatoid arthritis. If the eosinophil count rises above 5 per cent. the injections should be temporarily discontinued.^{6 16}

The importance to be attached to an erythematous or papular rash is rather doubtful. Forrestier¹² considered that it was not a contraindication to further injections; Freund and others have also expressed this view.^{13 11} Dameshek,⁵ who had reported a case of aplastic anaemia in a patient who had previously had erythema and desquamation, advises that this should be considered a sign for the utmost caution. Although we have examined the reports of seventeen cases occurring in the literature, we have only found one in which a preliminary erythema had been noted. Nevertheless, as erythema is a sign of intolerance to gold, we have adopted the practice of always stopping the injections when it occurs. On recommencing, half the previous dose is employed.

Summary

A fatal case of purpura haemorrhagica with agranulocytosis following gold injections is reported. The prophylaxis and treatment of such cases is discussed. The necessity for frequent haematological studies is emphasized.

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The British Institute of Philosophy has issued its programme of meetings to be held between October 15th, 1935, and May 7th, 1936. Addresses will be given by Sir Herbert Samuel, the Rev. Dr. Inge, Mr. C. E. M. Joad, the Dean of St. Paul's, Mr. H. A. L. Fisher, Professor Gilbert Murray, and Professor Ernest Barker. A syllabus can be obtained from the Director of Studies at University Hall, 14, Gordon Square, W.C.1.