The patient was discharged, symptom-free, on Oct. 1, 25 days after the onset of the illness, and 17 days after admission to hospital.

Comment

A patient suffering from a severe attack of psittacosis is usually ill for between two and four weeks. Prognosis is difficult to assess, but the outlook is better in the young than in the old, and extensive pulmonary involvement tends to carry a high mortality. In the patient under consideration penicillin therapy was started seven days after the onset, and complete defervescence had occurred 72 hours later. In view of the severity of his illness it seemed reasonable to attribute the satisfactory response to the treatment he received.

Reported cases of human psittacosis treated with penicillin are few. Parker (1945) published details of two such patients. In the first, a woman of 61, treatment with intramuscular penicillin in a dosage of 120,000 units daily was started on the nineteenth day of the illness, and the patient had become apyrexial on the twenty-first day. The second patient was a woman of 52 who received 160,000 units of penicillin daily from the thirteenth day. She was afebrile on the sixteenth day. In the same year Flippin, Gaydosh, and Fittipoldi (1945) treated a man of 53 with 100,000 units of penicillin daily after he had been ill for 19 days. On the twenty-second day great improvement was shown. However, since in these three patients the drug was given late in the disease, when spontaneous recovery might have been expected, the improvement which followed the administration of penicillin cannot conclusively be attributed to this treatment.

In the case of a patient aged 43 reported by Turgasen (1944) a daily dosage of 100,000 units of penicillin was begun on the fifth day of the illness. But the response was not dramatic, for the patient's high fever persisted for five days after the initiation of treatment. Rosebury *et al.* (1947) reported the treatment of a man aged 41 with both penicillin and sulphadiazine: 400,000 units of penicillin were given daily from the fourth to the fourteenth day of the illness, and 6 g. of sulphadiazine was given daily from the fifth to the twelfth day. The patient became apyrexial, and marked clinical improvement was shown as early as the sixth day, after he had received 800,000 units of penicillin and only 4 g. of sulphadiazine. The dosage of sulphadiazine here seems too small for this drug to have been of major therapeutic value, and the satisfactory response must therefore probably be attributed to the penicillin.

Wolins (1948) reported six patients suffering from psittacosis, only one of whom could be considered severely ill. Four of them responded satisfactorily, though not dramatically, to 400,000 units of penicillin daily. The same dose of penicillin had little effect on the course of the illness in the remaining two. Wolins pointed out that two of the four patients who responded well to penicillin had earlier failed to improve on a smaller dose (200,000 units daily).

In contrast with the clinical evidence there is good experimental evidence that infection of the mouse with psittacosis virus can be controlled by penicillin. Heilman and Herrell (1944) infected 104 mice with psittacosis virus and treated half of them with very large doses of penicillin (1,000 units daily), the remainder acting as controls. All the controls died, whereas the mortality in the treated mice was only 8%. This finding was confirmed by Bedson and May (1945), who also showed that the minimum dosage of penicillin necessary to protect a mouse from a lethal infection

was 800 units a day for four days. This again is a very large dose, and suggests that, if one may argue from mouse to man, the total dosage of penicillin needed to treat a human case of psittacosis would be about 11,000,000 units. The treatment of the case reported above was of this order.

It may be that the two most recent antibiotics, chloramphenicol and "aureomycin," which are effective against viruses of the psittacosis-lymphogranuloma group (Smadel and Jackson, 1947; Wright *et al.*, 1948), will prove more useful than penicillin. They have the added advantage that they can be given by mouth. However, neither is as yet available in this country, and in the meantime the encouraging result obtained in the case described here suggests that penicillin is well worthy of further trial in the treatment of psittacosis in man. It seems likely, however, that the dosage should always be massive; and if 2,000,000 units daily should prove ineffective an even higher dose should be considered.

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A CASE OF MONOCYTIC LEUKAEMIA TREATED WITH AMINOPTERIN

BY

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The acceleration of the leukaemic process produced by folic acid led to the search for antagonists which might favourably influence the disease. The most potent compound so far reported is "aminopterin" (4-aminopteroyl-glutamic acid), though others with similar properties have lately been used. It is effective in doses of 0.5–1 mg. daily in children and up to 4 mg. daily in adults. It causes a general depression of bone-marrow function and has toxic effects at therapeutic dosage which seriously limit its usefulness. It can be given by intramuscular injection, but is equally effective by mouth. In the case reported below none was available for oral administration.

Case Report

An obese man aged 30, who was subject to spasmodic bronchitis severe enough to warrant grading C2 in the Army, presented with a six-weeks history of furunculosis and stomatitis. For six months he had been listless and unduly fatigued. The stomatitis consisted of a boggy hypertrophy of the gums and hard palate. There was no bleeding, but the mouth was very painful. Neither spleen, liver, nor lymph glands could be felt to be enlarged. There was an irregular fever; the patient was anaemic, and Hess's test for capillary fragility was positive. A blood count showed: white cells 32,400 per c.mm. (monocytes

62%, lymphocytes 28%, polymorphs 10%); red cells, 2,700,000 per c.mm.; Hb, 48%. Sternal marrow puncture showed 73% of the cells to be monocytes or precursors, with numerous primitive cells. A diagnosis of Schilling-type monocytic leukaemia of subacute nature was made. The marrow counts are shown in the accompanying table.

Table Showing Marrow Counts

	Day		
	3rd	44th	62nd
Neutrophil myelocyte	5%	28%	35%
Eosinophil myelocyte			
Neutrophil polymorph	6%	20%	11%
Eosinophil polymorph			
Monocytes and precursors	73%	19%	29%
Lymphocytes	12%	9%	5%
Nucleated red cells	2%	23%	11%
"Blasts"	2%	1%	4%
Plasma cells	—	—	1%

Treatment was begun with fresh blood transfusions and penicillin, which improved the local sepsis and general condition. Aminopterin was first given on the thirteenth day, and an immediate improvement occurred in the peripheral blood count (see Chart). The platelets were only 37,000 per c.mm. at first, but this level was well maintained throughout treatment. There

Chart showing progress of case.

was one brief intermission due to a respiratory infection, but apart from this the remission progressed until the blood picture was normal. A second sternal puncture showed a great improvement in the balance between the cells and considerable maturation.

Thirty-two days after starting treatment, when 64 mg. of aminopterin had been given, the toxic effects of the drug became manifest. Stomatitis due to painful shallow ulceration of the gums, spreading on to the lips, became steadily worse until treatment had to be stopped. A total of 109 mg. had then been given. The stomatitis rapidly healed on ceasing treatment.

A slow tendency to relapse was manifested in the peripheral blood picture even before treatment was stopped, but afterwards a rapid multiplication of the leucocytes occurred, the pathologist remarking that the blood resembled a marrow smear in the number of primitive cells involved. Between the 71st and 80th days the patient was at home, but on return to hospital the blood was found to contain 125,000 white cells per c.mm. (77% monocytes and 5% promonocytes)—a picture far more mature than during the rapid multiplication period after the aminopterin was stopped.

A second course of the drug was given, with blood transfusion; this led to a second and more dramatic remission, but the toxic effects of the aminopterin recurred almost immediately and the treatment was again stopped. Toxicity on this occasion

also involved colicky abdominal pain, diarrhoea, and ulceration of the rectum. On the 103rd day, when the blood picture had again become grossly leukaemic, the patient was given a massive transfusion without aminopterin; but no improvement occurred, showing that transfusions were probably not the cause of the remissions. It was intended to follow this by a course of aminopterin without blood, but on the 113th day the patient died suddenly, almost certainly from a pulmonary embolism from a site of transfusion in the leg, although he was ambulatory up to the last. Only a limited post-mortem examination was permitted, so that it was not possible to confirm the immediate cause of death.

Comment

This case is of interest, as Dameshek (1949) was unable to produce remissions in three cases of monocytic leukaemia treated by him with folic acid antagonists, though myeloid and lymphoblastic cases responded. The readiness with which a return to maturity may be induced in the leukaemic cell with aminopterin serves to remind one that the leukaemic states are in the borderland between neoplastic and infective disease.

Leukaemic cells differ from cancer cells in that they do not show the phenomenon of aerobic glycolysis (Kempner, 1939); also they mature within 14 days when cultured *in vitro* (Israëls, 1940), whereas cancer cells multiply unchanged indefinitely. Mouse and fowl leukaemias are readily transmissible, but there is reason for suspecting that these results may be inapplicable to human leukaemia, since the disease has never successfully been transmitted in mammals other than rodents. The demonstration of marrow-stimulating substances in large quantities in the urine and faeces of leukaemic patients (Miller and Turner, 1943) suggests that the basic error in leukaemia may lie not in the leukaemic cell but in its environment. The ultimate cause of this change is unknown, and on that point it is difficult even to conjecture. But this concept provides a far more fruitful line of possible therapy, since, if the environment can be altered, useful remissions should be obtainable. Perhaps aminopterin may represent this form of approach to the problem: its effectiveness in such small quantities suggests that it may be acting on a fundamental mechanism. The efforts to obtain more effective and less toxic drugs of this nature which are now in progress are therefore amply justified.

Summary

A case of monocytic leukaemia in a man aged 30 is described in which remissions followed the administration of aminopterin. The peripheral blood count returned entirely to normal after five weeks, but owing to toxicity the drug had to be withdrawn after 109 mg. had been given, and a rapid relapse followed. A further remission was obtained by a second, shorter, course. The patient died on the 113th day from pulmonary embolism. Some aspects of this form of therapy are discussed.

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