AGRANULOCYTOSIS FOLLOWING CHEMOTHERAPY WITH SMALL DOSAGE

BY

ALEX W. SPAIN, M.A.O., M.R.C.O.G.

Mater Misericordiae Hospital, Dublin

Many cases of agranulocytosis following sulphapyridine and sulphanilamide therapy have been published. According to L. Colebrook (*Journal*, March 16, p. 450) more than fifty cases had been reported in the last two years. He says: "The particulars of published cases strongly suggested that this dangerous condition (it had a mortality rate of about 50 per cent.) was closely related to the amount of drug given and the duration of treatment. The average total dose in the recorded cases had been 50 grammes and the duration of treatment twenty days." The case here reported is worthy of record on account of the small dosage (4.5 grammes of sulphapyridine and 4.5 grammes of sulphanilamide), the short duration of treatment (four days), and the fact that despite early diagnosis and prompt treatment it proved fatal.

* Case Report

A primipara aged 26 had a lower-segment Caesarean section performed on February 5, 1940, before labour had started. The blood loss was moderately heavy. Convalescence was uneventful until February 12, when a rash resembling that of rubella developed. In the evening the temperature rose to 101° F. The rash disappeared within thirty-six hours, but the temperature was again 101° F. on the evening of February 13. A small haematoma was now discovered at the lower end of the wound; this was opened with a dressing forceps and a small quantity of clot and pus evacuated.

On the morning of February 14 (tenth day after operation) her temperature was again 101° F., and she now complained of tenderness in the outer and lower quadrant of the right breast. Antiphlogistine applications were ordered to the breast, and the patient was given a tablet of sulphapyridine (0.5 gramme) every sixth hour. Next day the affected part of the breast was hard and tender and the evening temperature was 103° F. Treatment with local applications was continued, but a change was made to sulphanilamide 0.5 gramme every hour. (This change was made inadvertently.) On February 16 she felt better and the breast was less hard and tender. Her temperature had dropped to 99° F. and her pulse was 80. It appeared that the mastitis was subsiding without abscess formation. Chemotherapy was continued for a further two days. From February 14 to 18 she received 4.5 grammes of sulphapyridine and 4.5 grammes of sulphanilamide.

The patient continued to improve, and appeared almost to have recovered from the mastitis by February 20. All tenderness of the breast was gone, though there was still some thickening. She now felt quite well and was hoping to be allowed up in a day or two.

When seen on the morning of the 21st she complained of a slight "sore throat" and her temperature was 102° F. At the time an epidemic of influenza, of which "sore throat" was a marked feature, was widespread in the city. It was considered that she had developed "influenza." Her temperature at 6 p.m. on the same day was 99.4° F. and pulse rate 100; she still complained of the throat, though no lesion could be seen. She looked rather more ill than she should if her condition was influenza. The possibility that the condition was agranulocytosis was considered, but this was regarded as very improbable in view of the small dosage and the similarity of the symptoms to those of the epidemic of influenza. However, her appearance was not satisfactory, so I got in touch with Professor McGrath with a view to having a blood examination made. That evening she had a rigor at 7.30 and her temperature rose to 105° F. It fluctuated around this level until her death four days later.

A blood count done by Professor McGrath at about 9.30 p.m. showed marked agranulocytosis with severe secondary anaemia (see table). Within an hour of the receipt of the report on her blood she was given 10 c.cm. of pentnucleotide intramuscularly. This was followed immediately by a transfusion of 450 c.cm. of citrated blood, and one hour later she received a further 10 c.cm. of pentnucleotide. Subsequently

Table showing Daily Blood Counts

Date	Red Cells (millions per c.mm.)	Haemo- globin	Colour Index	Leuco- cytes per c.mm.	Lymphocytes		Neutro- phils	Other Granu- lar Cells
					Small	Large		
Feb. 21	2.49	36	0.7	1,920	21	77	1	1
" 22	2.29	42	0.9	1,280	40	58	1	1
" 23	1.89	45	1.2	960	20	76	1	3
" 24	2.54	50	1.0	960	34	62	2	2
" 25	3.27	65	1.0	1,280	17	24	59	0

during her illness she was given 10 c.cm. of pentnucleotide every sixth hour, save in the last twenty-four hours, when it was administered every five hours. Thus in the first twenty-four hours she received 50 c.cm. of pentnucleotide, in the second twenty-four hours 40 c.cm., in the third twenty-four hours 40 c.cm., and in the last twenty-four hours 50 c.cm. In addition she was given two further transfusions of citrated blood, each of about 450 c.cm., on the second and third days of the agranulocytosis. Daily blood counts were made (see table). The leucocytes numbered 1,920 on the first count (February 21); by February 23 they had fallen to 960, and on February 25 had risen again to 1,280. The neutrophils, which were only 1 per cent. of the total white cells at the first count and which remained at this level for three days, constituted 59 per cent. of the total white cells on February 25.

In spite of active treatment and her response to pentnucleotide she died on the fifth day of her illness. Her clinical condition had become steadily worse, and on no occasion showed any tendency to improve.

CONDITION OF THROAT AND PALATE

February 21: No lesion obvious; soreness complained of by the patient. February 22: A few small vesicles, about the size of the head of a large binder pin, were observed on the right side of the soft palate and on the right tonsil. February 23: The vesicles were now seen all over the soft palate. February 24: The vesicles were replaced by whitish patches. This appearance was also present on the 25th, the day of death. No evidence of oedema of the throat or larynx was observed at any time.

I am greatly indebted to Professor John McGrath, M.D., for the blood examinations and for much helpful advice. I am also indebted to Mr. Andrew L. Butler, M.Ch., for advice about the blood transfusions, which he administered.

St. Andrew's Hospital for Nervous and Mental Diseases at Northampton, according to its report for 1939, admitted 166 patients during that year, and its average daily number was 500 patients, certified, voluntary, and temporary. In spite of a state of emergency the work has proceeded without interruption. The medical superintendent, Dr. Thomas Tennent, mentions the use of insulin and cardiazol in the treatment of cases of schizophrenia. Since the treatment by insulin was introduced in August, 1938, twenty patients have received a full course. The variation in the response to the dosage of insulin was noteworthy. In one patient the method was abandoned, as 1,000 units failed to produce coma. Of the twenty patients, eight improved clinically to such an extent that it was possible for them to return home, and some degree of improvement was noted in the remainder. Forty patients suffering from schizophrenia received one or more courses of cardiazol, and of this number one-half improved clinically to such a degree as to make it possible for them to leave the hospital, and according to the most recent reports their improvement has been maintained.