AGRANULOCYTOSIS FOLLOWING SULPHAPYRIDINE THERAPY

BY

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The occasional occurrence of a dangerous and sometimes fatal granulocytopenia during treatment with sulphanilamide preparations is now well recognized, and many cases have been recorded. Reports of this condition occurring during the administration of the allied drug sulphapyridine (M & B 693) are perhaps still rare enough to justify this short review and case report.

Cases in the Literature

Since the publication of the first description by Johnston (1938) there have been, so far as we can ascertain, eight further recorded cases. This total does not include those occurring in young children (Dolgopol and Hobart, 1939; Hodes *et al.*, 1939) or the case mentioned but not fully described by Melton and Beck (1939). As might be expected in view of the wide application of the drug, the primary disease varies, being lobar pneumonia in two (Tzanck *et al.*, 1939; Agranat *et al.*, 1939), streptococcal septicaemia in two (Johnston, 1938; Sutherland, 1939), puerperal pyrexia in two (Briggs, 1939), thrombophlebitis during typhoid in one (Coxon and Forbes, 1938), appendix abscess in one (Barnett *et al.*, 1939), and gonococcal epididymo-orchitis in one (Nichol and Freedman, 1939).

The dosage and duration of treatment with sulphapyridine also vary widely, ranging from the 18 grammes in fifteen days of Tzanck's case, where idiosyncrasy to the drug was strongly suggested, to the 80.9 grammes in seventeen days administered by Barnett. The average dose throughout the series is 53 grammes, and the average duration fourteen days. This bears out the suggestion of Sutherland that doses of over 50 grammes are dangerous, especially to patients already suffering from a disease causing blood destruction.

Time of Onset

The exact time at which the white cell count begins to fall is often difficult to determine. In some of the recorded cases serial counts showed that an alarming fall did not occur until some days after the drug had been withdrawn. This suggests that the frequent counts advocated by so many may not give warning in time to prevent the occurrence of a dangerous granulocytopenia. Strict limitation of dosage and the realization of the possible significance of a secondary rise of temperature may be the only safeguards against this complication in the future, although even this will not eliminate the cases due to idiosyncrasy. The degree of reduction of the granulocytes was extreme in all the cases mentioned except one of those reported by Briggs. In most of them granular cells were completely absent. The lowest total leucocyte count was found in Barnett's case (75 per c.mm.), and in the majority the count was 2,000 or less. Ulceration of the fauces occurred to a marked degree in three cases only.

Treatment of Agranulocytosis

Treatment in all cases consisted in blood transfusion and administration of pentnucleotide. In some of the non-fatal cases improvement followed after a period of several days, suggesting that the treatment was effective; but in others, as in the case reported here, it seemed that the rise in the white cell count was so immediate as to appear merely coincidental. There were four fatal and five non-fatal cases in the series under review, but in Johnston's fatal case blood culture repeatedly gave a growth of *Streptococcus viridans*, and fresh vegetations were found on the tricuspid valve at necropsy, while the immediate cause of the death of Barnett's patient was haemorrhage from an incised cervical gland and from the pharynx. The remaining two fatal cases had certain exceptional features, so the prognosis in this condition is perhaps not so grave as might be imagined.

Case Report

An unmarried woman aged 54, with a good previous history, was seen by one of us (R. H. M.) on the third day of illness; she complained of general malaise, cough, and pain over the base of the left lung. The temperature was 102° F., pulse 126, and respirations 36. Signs of pneumonic consolidation involving both upper and lower lobes of the left lung were found, and a pleural rub was heard at the left base. The expectoration was blood-stained. A diagnosis of massive left lobar pneumonia was made, and treatment with sulphapyridine started, the dosage being 5 grammes daily for the first three days. The temperature fell to below normal on the fifth day of the disease (the third day of treatment), and on the sixth day the dosage was reduced to 2.5 grammes daily.

The patient's condition remained good until the end of the eighth day, when treatment with sulphapyridine was stopped, 22.5 grammes of the drug having been given in six days. On the tenth day the temperature began to rise, reaching 102° on the evening of the eleventh day. She was seen in consultation by one of us (B. P.) on the following day. Her general condition was still good, but she complained of severe pains in the legs. The temperature was 101°, pulse 110, and respirations 28. Examination revealed signs of consolidation of the left lung and a pleural rub in the left axilla at the level of the fifth rib. Apart from some oral sepsis, no cause for the secondary rise in temperature could be found, and it was decided to continue treatment with sulphapyridine (2.5 grammes daily) and to watch carefully for any sign of empyema or other complication.

On the seventeenth day of illness the general condition remained unchanged, but pyrexia continued and the patient was seen again in consultation (B. P.). The extent of the consolidation appeared less, but no signs of resolution were present. As the breath sounds were somewhat diminished at the left base paracentesis was performed; but only air was obtained, the needle having apparently entered either a small pneumothorax or the substance of the lung, though the latter would seem unlikely in view of the pneumonic condition. The dosage of sulphapyridine was now reduced to 1.5 grammes daily, and it was decided to move the patient from the country to a nursing home where radiological and bacteriological facilities would be available. For the next few days the condition appeared to be improving and the pyrexia diminished, but on the twenty-fifth day of the disease the transfer to a nursing home was made and treatment with sulphapyridine stopped. The total dosage was 46.5 grammes over a period of eighteen and a half days.

EXAMINATION

Radiological examination to exclude interlobar empyema was made by Dr. T. Garratt Hardman, with negative results, the film simply showing a basal opacity suggestive of unresolved pneumonia. Blood culture, examination of a swab from the gums, and blood counts were then carried out (G. C. D.). The culture was sterile, and the swab showed no pathogenic organisms, but the blood count revealed under 200 white cells per c.cm. (see Table), with a complete agranulo-

cytosis. There were 2,340,000 red cells per c.mm. and the haemoglobin was 45 per cent.

Table showing the White Cell Counts

Date	Total Leucocytes	Polymorphs. %			Baso. %	Myelo. %	Meta-myelo. %	Lymph. %	Mono. %
		Stab.	Seg.	Total					
Nov. 26	Under 200	0	0	0	0	0	0	95	5
" 29	9,200	—	—	32	0	—	3	62	3
Dec. 2	20,000	26	22	48	1	2	5	35	9
" 5	9,400	0	64	64	0	0	0	35	1
" 19	11,600	0	60	60	0	0	0	38	2

It is noteworthy that it was only now, on the twenty-seventh day of the illness and two days after the drug had been withdrawn, that any ulceration of the mucous membrane of the throat or mouth developed. This took the form of three minute vesicles on the palate and a small ulcer beneath the upper lip. These lesions healed in four days. The throat remained normal in appearance throughout.

TREATMENT

A transfusion of half a pint of citrated blood was given (G. C. D.) and pentnucleotide injections were started, 30 c.cm. being given on the first day, 20 c.cm. on the next three days, and 10 c.cm. on the fifth day. The clinical improvement was dramatic. The temperature began to fall, and reached normal on the third day after the transfusion. A white cell count performed two days after the beginning of treatment gave a total of 9,200 per c.mm., with 32 per cent. polymorphs. Lymphocytes, which constituted 95 per cent. of the first count, had now fallen to 62 per cent., and metamyelocytes had made their appearance (3 per cent.). Three days later there was a further rise in the total count, to 20,000 per c.mm.—polymorphs 48 per cent., lymphocytes 35 per cent. After a further three days the count was normal, with the exception of a slight leucocytosis (9,400). The red cell count was now 2,620,000 per c.mm., and the haemoglobin 55 per cent.

The patient has made an uninterrupted recovery. Iron and liver extract are being administered for the hyperchromic type of anaemia which is present. The most recent blood count (December 19, 1939) shows the red cells to have risen to 3,470,000, and the haemoglobin to 70 per cent. A leucocytosis of 11,600 remains, with a normal differential white cell count. Poikilocytosis and anisocytosis are present to a slight degree.

The following points of interest arise in connexion with this case history: (1) the rapid recovery of the patient, in spite of the fact that the diagnosis was not made until there was a complete absence of granular cells in the blood; (2) the absence of "angina," with the exception of the slight ulcerative changes in the mouth; (3) the single symptom of persistent severe pain in the legs; and (4) the absence of any evidence of other toxic reaction to the drug.

Summary

Previously reported cases of agranulocytosis during sulphapyridine therapy are briefly reviewed.

A similar case is described in which the blood condition is attributed to the treatment of pneumonia with sulphapyridine, no other drug known to cause agranulocytosis having been administered.

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Clinical Memoranda

The Use of Dried Diphtheria Antitoxin

On a former occasion I showed that concentrated (globulin only) diphtheria antitoxin when given intravenously was followed by immediate rigors and hyperpyrexia in 23 per cent. of the cases (Peters, 1938). Whole natural antitoxin, although four times the volume of the concentrated antitoxin and containing all the foreign proteins of the horse, gave only 1.1 per cent. of similar reactions. The one disadvantage of the whole serum was the greater bulk of the injection.

By the courtesy of Messrs. Sharp and Dohme I have had the opportunity of trying a dried whole antitoxin. This is stated to be dried by rapid freezing and dehydrating under high vacuum until the moisture content is under 1 per cent. The material consists of a bulky powder which rapidly dissolves on adding 15 ml. of distilled water to the phial, which contains 50,000 units of antitoxin. This is about one-fifth of the volume of an average sample of unconcentrated natural antitoxin, but it still contains all the elements present in the whole horse serum.

The twenty cases selected for trial all had very severe attacks of diphtheria; seventeen of them had bull necks, five were second-day cases, five third-day, seven fourth-day, two fifth-day, and one a sixth-day case. During the period of this test almost all our admissions were due to a virulent intermediate strain of *Corynebacterium diphtheriae*. The antitoxin was administered intravenously, diluted with 90 to 150 ml. of 20 per cent. glucose, as is our custom in such cases. Not one of the cases had any immediate reaction, eleven had late serum rashes of moderate severity, and only two deaths occurred—one from circulatory failure on the tenth day and another from paralysis of the diaphragm in the sixth week. This is a very favourable death rate in these severe cases, being one-half that of my former but much larger series, to which I have already referred; but as the present series is small the difference is not statistically significant.

It would therefore appear that antitoxin in this form is highly suitable for intravenous injection owing to its apparent lack of rigor-producing properties and its small bulk, while its therapeutic effects are at least equal to those of any other antitoxin. A more extensive trial might show that it was better than precipitated and redissolved, globulin only, antitoxin. I note that Dr. J. C. McSweeney (1939) stated that something more potent than the existing commercial antitoxin was required in order to ensure a minimum mortality rate. Some such preparation as the one here tested may meet the case, as this rapidly cooled and dried material may undergo less alteration from its original state and would be less liable than any liquid form to deterioration on keeping. This fact is proved with many of the enzymes and toxins.

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