AGRANULOCYTOSIS AND PARA-AMINO-BENZENE SULPHONAMIDE

BY

C. J. YOUNG, M.B., D.T.M., D.P.H.

(From the Pathological Department, Bradford Royal Infirmary)

Kracke and Parker (1933, 1934) presented evidence that agranulocytosis might be caused by certain drugs, notably amidopyrine, phenacetin, certain gold salts, and arsphenamine. They pointed out that structurally these drugs possess in common the benzene ring with an attached NH_2 or amine group, which increases the ease of oxidation. A consideration of the formula of sulphanilamide suggested to us the possibility that this drug might

also be capable of producing agranulocytosis. The matter appeared to be one of importance for various reasons. First, if the drug reduced the polymorph concentration in the blood in cases of infection against which it was therapeutically ineffective, it might affect unfavourably the course of the disease. Secondly, sulphanilamide is used in acute infections which are not infrequently fatal, and where the latter outcome resulted from agranulocytosis this might readily escape observation. Thirdly, the drug is available to the general public and has received considerable publicity in the lay press.

It was decided, therefore, to make observations on the leucocytes in sulphanilamide-treated patients. Complete agranulocytosis with fatal result occurred in the second case investigated. While the possibilities are obvious, it naturally cannot be determined whether this occurrence was or was not due to the administration of this drug.

Case of Agranulocytosis

The patient was a man of 53 suffering from acute rheumatism with joint pains and pyrexia. There was a history of previous attacks in 1901, 1908, and 1914. The condition failed to respond to salicylates, and prontosil album (3 grammes daily for eighteen days) was given. At the end of this period the clinical condition had deteriorated, the temperature running at a higher level than before, and treatment was stopped. Four days afterwards complete agranulocytosis was found, and blood culture, which had given no growth three weeks pre-

TABLE I.—Drugs administered

Date	Drug	Dosage
8–11/4/37	Sodium salicylate	60 grains daily
18–23/4/37	"	60 " "
12 and 18/4/37	Aspirin	50 " "
26/4/37	"	30 " "
3–21/5/37	Prontosil album (orally)	3 grammes "
13/5/37	Medinal	7½ grains
14/5/37	Veronal	10 "
19/5/37	Chloral	10 "
20/5/37	Veronal	10 "
25/5/37	Chloral	10 "
"	Pentnucleotide	0.7 gramme
26/5/37	Veronal	10 grains

vously, now gave haemolytic *Staphylococcus aureus* and *Streptococcus viridans*. The patient died the following day.

The treatment administered is summarized in Table I, and the haematological observations in Table II.

TABLE II.—Blood Counts

		Dates							
		5/5/37	7/5/37	11/5/37	14/5/37	20/5/37	25/5/37	26/5/37*	
Haemoglobin	..	90						82	per cent.
Leucocytes	..	12,000	9,800	8,200	9,700	7,800	1,800	2,300	„c.mm.
Polymorphs	..	6,600	5,047	4,633	6,984	5,694	0	0	„ "
Lymphocytes	..	4,344	3,577	2,214	2,085	1,755	1,800	2,300	„ "
Monocytes	..	660	784	861	388	351	0	0	„ "
Eosinophils	..	396	392	410	194	0	0	0	„ "
Basophils	..	0	0	41	0	0	0	0	„ "
Myelocytes	..	0	0	41	49	0	0	0	„ "
Arneth Count	I	32	32	41	59	58	0	0	„ cent.
	II	45	44	41	34	34	0	0	„ "
	III	21	24	17	7	8	0	0	„ "
	IV	2	0	1	0	0	0	0	„ "
	V	0	0	0	0	0	0	0	„ "
Lobes per 100 polymorphs	..	193	192	178	148	150	0	0	„ "
Classes I + II	..	5,082	3,800	3,772	6,510	5,244	0	0	„c.mm.
Degenerative index †	..	0	0	0	0	2	—	—	„ cent.

* 26/5/37, post-mortem counts, three hours after death : red cells, 4,290,000 ; reticulocytes, 75,000 ; platelets, 141,000 per c.mm.

† Percentage of polymorphs showing toxic granulation.

All counts were made about the same time each morning.

Skin rashes occurred on April 14 and May 12, 21, and 24. Traces only of albumin were found in the urine on four occasions.

Post-mortem Findings

The post-mortem examination was made three hours after death. An inflammatory lesion covered with greyish-white membranous exudate was present in the pharynx, showing a patchy distribution over the sides and posterior surface of the pharynx and posterior surface of the epiglottis. The membrane consisted of the necrosed superficial tissues infiltrated with masses of cocci. Collections of lymphocytes were present but no polymorphs. Bacteriological examination showed the predominating organisms to be haemolytic *Staphylococcus aureus* and *Streptococcus viridans*, and was negative for diphtheria.

The blood in the heart was not coagulated, so allowing counts to be made. A few minute nodules due to simple non-ulcerative endocarditis were present on the mitral valve and were presumably of rheumatic origin ; no bacteria were observed in them.

The right kidney showed a moderate hydronephrosis due to an aberrant artery, but only slight damage to the renal structures was found microscopically. The liver (1,555 grammes), spleen (175 grammes), and other organs revealed nothing of note.

Bone Marrow.—The distribution of red marrow was normal, being present in vertebra, sternum, and ribs, while that in the right tibia and femur was fatty, only the head of the femur and upper part of the shaft showing some pink coloration. Microscopically there was a complete absence of all granular cells, both neutrophil and eosinophil, while cells of the lymphocyte series, mega-

karyocytes, and nucleated red cells were numerous in the red marrow. Spectroscopic examination of the blood for sulphaemoglobinaemia was negative. Death was considered to be due to agranulocytic angina with septicaemia.

Discussion

Between May 3 and 21 54 grammes of prontosil album were given. Agranulocytosis developed some time between May 20 and 25. A feature of the case was the failure of serial leucocyte counts to give warning of the impending disaster, the changes being merely those of a progressively active infection. An increased output of young polymorphs (Arneth classes I + II, Table II) was well maintained till May 20, after which a rapid failure in their production evidently occurred. The types of myeloid bone marrow found in cases of agranulocytosis include aplastic, normal, and hyperplastic varieties (Beck, 1933). The present case belongs definitely to the aplastic type.

Of the various drugs administered, chloral and the barbiturates do not contain the benzene ring. Barbiturates have been frequently used in association with amidopyrine in recorded cases, and an adjuvant effect has been suggested, but available evidence is against their being independently effective. Salicylates contain the benzene ring with no amino group; there is little evidence that they can cause agranulocytosis, and in any case none had been given within twenty-four days of the onset of the condition. Kracke (1932) produced experimental agranulocytosis in rabbits with benzene, but concluded that oxidation products were probably responsible. Kracke and Parker (1934) later recorded that there was constantly increasing evidence that the condition was caused for the most part by easily oxidizable benzene-ring drugs.

Marshall, Emerson, and Cutting (1937) have investigated the excretion of sulphanilamide, and found that 100 per cent. of the daily dose could frequently be recovered in the urine as free sulphanilamide and a conjugated form—para-acetylaminobenzene sulphonamide. They add, however, that it is possible under certain conditions that a small amount is excreted in some other form or eliminated through some other channel than the kidneys. They showed in a case with impaired renal function that there was delay in excretion of the drug.

Cases of agranulocytosis have been recorded in which no drugs appear to have been taken and no obvious cause could be found, so that a definite conclusion in regard to the causation in the present case is not justified.

Summary

1. A case of fatal agranulocytic angina is recorded.
2. The bone marrow showed complete myeloid aplasia.
3. The only benzene-ring drug administered within twenty-four days of the development of agranulocytosis was sulphanilamide.
4. The agranulocytosis appeared to be either of the idiopathic type of unknown aetiology or to be due to sulphanilamide.

I am indebted to Dr. J. K. Rennie for the clinical material and data, and to Dr. J. A. Price and Mr. G. C. Holliday for assistance with some of the investigations.

REFERENCES

- Beck, R. C. (1933). *Arch. intern. Med.*, **52**, 239.
 Kracke, R. R. (1932). *Amer. J. clin. Path.*, **2**, 11.
 ——— and Parker, F. P. (1933). *J. Lab. clin. Med.*, **19**, 799.
 ——— (1934). *Amer. J. clin. Path.*, **4**, 453.
 Marshall, E. K., Emerson, K., and Cutting, W. C. (1937). *J. Amer. med. Ass.*, **108**, 953.

FOOD POISONING—ITS EPIDEMIOLOGY AND BACTERIOLOGY*

BY

E. R. JONES, M.D., D.P.H., F.I.C.

Senior Pathologist, Kent County Council

The term "food poisoning" is conventionally restricted to an acute gastro-enteritis caused by the ingestion of food or drink which either contains living bacteria capable of setting up an acute inflammatory condition of the alimentary tract or contains toxic substances produced by various types of bacteria that have an irritant effect upon the gastro-intestinal mucosa. This definition does not include "botulism," a disease which presents no symptoms of gastro-enteritis, but which is nevertheless a form of food poisoning caused by the absorption from the alimentary canal of a specific toxin elaborated under suitable conditions by the *Clostridium botulinum*.

During recent years the number of organisms proved to be capable of giving rise to food poisoning in one or other of its forms has greatly increased. Since the isolation of *B. enteritidis* by Gaertner in 1888—followed ten years later by the isolation of *B. aertrycke*, or *Bact. typhi murium* as this organism is now called, by Durham in England and de Nobele in Belgium, both organisms being undoubtedly responsible for cases of food poisoning—at least twenty-seven members of the Salmonella group have been identified with actual outbreaks of food poisoning in human beings. It is of importance to note, too, that some pathogenic intestinal organisms normally giving rise to one particular type of disease may on occasion cause another kind of illness—for example, the dysentery organisms may produce the typical symptoms of food poisoning.

It is difficult to assess with any degree of accuracy the prevalence of food poisoning. Many solitary cases must undoubtedly go undetected, but with increased laboratory facilities such cases are being detected with greater frequency. In some form or other cases occur fairly often in this country—for example, fifty-eight outbreaks were recorded at the Ministry of Health in 1934, and of 137 outbreaks of suspected food poisoning in 1935 only twelve were excluded as not food poisoning. In America and Germany the incidence seems to be considerably higher.

Food poisoning may be conveniently discussed under three headings: (1) that due to the multiplication within the body of pathogenic bacteria present in food, and referred to as the "infection" type; (2) that due to the ingestion of certain substances formed as the result of bacterial multiplication in the food before ingestion—the "toxin" type; and (3) that due to the toxin of *Clostridium botulinum*—"botulism."

The "Infection" Type

Among the organisms responsible for the "infection" type members of the Salmonella group are the most common, but members of the dysentery group, more especially the Sonne bacillus and *B. dysenteriae* Flexner, must be included. In 1934 Salmonella infections were discovered in twenty-two instances, of which fourteen were, so far as could be ascertained, solitary cases, and during 1935 these were found on fifty-three occasions; twelve outbreaks during the latter year, however, were caused by dysentery bacteria, of which eight were due to the Sonne bacillus, three to *B. dysenteriae* Flexner, and

* Paper read at the Congress of the Royal Institute of Public Health and Institute of Hygiene, Margate, 1937.