ACUTE AGRANULOCYTOSIS*

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In 1922 Werner Schultz[1] described a clinical entity characterized by sudden onset, severe and rapidly progressive necrotic lesions in the pharynx, a profound constitutional disturbance, a marked reduction in the number of circulating neutrophils, severe toxaemia and death.

Turk[2] had recognized the condition as early as 1907. The condition described is acute agranulocytosis.

Not only are the necrotic lesions noted in the pharynx, but there can also be sloughing in the vagina, in the gastro-intestinal tract, the respiratory tract and of the skin. The leucocyte count may be as low as 250/cu.mm. with the disappearance of polymorphs, while the red cell count remains normal.

Kracke[3,4] in 1931 attributed the increased incidence of this condition to the increasing use of coal tar derivatives as therapeutic agents, and in 1933 Madison and Squier[5] reported on amidopyrine as a cause of the condition.

Since drug administration was first blamed for the occurrence of agranulocytosis and for other blood dyscrasias, the numbers of drugs and combination of drugs which have been incriminated has grown. The Sub-committee on Blood Dyscrasias of the American Medical Association has listed more than 450 such drugs.[6,7]

Cyclic neutropenia was described by Reiman and De Baradinis[8] in 1949, and primary splenic neutropenia and chronic hypoplastic neutropenia have also been described,[9] but would not appear to be related to the acute agranulocytosis dealt with in this report.

A case of fatal pneumonia, attributed to *Achromobacter anitratus*—an organism not usually considered pathogenic—and associated with profound neutropenia, has recently been reported by Stockwell *et al.*[10] I have found blood culture of little or doubtful value when dealing with acute

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agranulocytosis. Organisms are frequently found which are there as a result of the agranulocytosis, and such organisms are unlikely to be a cause of the condition.

I am satisfied that all but one of the cases I have seen were caused by *drug hypersensitivity*. The reaction develops after 7 - 10 days' administration of the drug or occurs on the initiation of a further course of therapy. This type of sensitization has been most thoroughly documented in the case of amidopyrine, but can also occur with other drugs as described by Douglas.[11] I have not seen a typical case of acute agranulocytosis with profound toxaemia and death which could not be attributed to a drug containing amidopyrine.

TABLE I. FATAL CASES OF AGRANULOCYTOSIS SEEN BETWEEN 1924 AND 1965

Year	*Race*	*Age*	*Sex*	*Onset of symptoms*	*Drug causing the condition*
1926	E	64	M	Gradual	Neo Salvarsan (arsenic)
1934	E	15	F	Sudden	Veramon (amidopyrine)
1934	E	24	M	Sudden	Veramon (amidopyrine)
1936	E	22	F	Sudden	Veramon (amidopyrine)
1938	E	45	F	Sudden	Veramon (amidopyrine)
1963	E	71	F	Sudden	Orfenso (amidopyrine)

The case seen in 1926 was not typical in that the onset of the toxaemia was gradual. The patient was a medical practitioner, and both he and the attending physician had great faith in the value of arsenicals and an excessive enthusiasm for this form of therapy, well remembered by those of us who practised medicine before the antibiotic era. This was an avoidable death.

I have seen severe neutropenia with necrotic pharyngeal lesions caused by drugs other than amidopyrine, but these were neither explosive in onset nor fatal.

TABLE II. NON-FATAL CASES OF NEUTROPENIA, PYREXIA AND PHARYNGEAL ULCERATION

Year	*Race*	*Age*	*Sex*	*Onset of symptoms*	*Drug causing the condition*
1935	E	29	M	Gradual	Veramon
1936	E	51	F	Gradual	Veramon
1939	E	17	F	Gradual	Sulphanilamide
1939	E	70	F	Gradual	Veramon
1946	E	49	F	Gradual	Veramon

I have noted the development of neutropenia while a patient was under treatment with sulpha drugs, antithyroid drugs and with phenylbutazone. Such cases are well known and well documented, and the careful physician prescribes certain drugs with a full knowledge of the risks involved. The patient must be kept under strict observation and the medication stopped on the first evidence of leucopenia and on the first symptoms which may suggest that all is not well.

There is a risk involved in the use of many valuable and occasionally essential drugs. Chloramphenicol may be essential in the treatment of typhoid and in other conditions and must be used even though it is reported to have caused aplastic anaemia. Phenylbutazone (Butazolidine) can be most useful and should not be withheld on account of the risk of neutropenia, but amidopyrine is dangerous. A sensitization reaction can develop rapidly, cannot be controlled, and is usually fatal. It is never essential to use amidopyrine.

TREATMENT

Massive doses of antibiotics must be used and the newer penicillins, particularly ampicillin, are probably best.

Steroids should be used in large doses though there is some doubt whether they are really of value.

Intravenous fluids may be necessary. As there is no anaemia there is no need for additional blood or additional haemoglobin, but repeated small transfusions should be used on the assumption that they may be of value.

The patient must be shielded from any new risk of infection and, most important of all, other patients and attendants must be protected from the many virulent organisms which flourish in the absence of polymorph nuclear cells.

PROGNOSIS

When the white-cell count is below 1,000 cells/cu.mm. and the granulocytes below 20%, the prognosis is extremely grave, but recovery is possible in the younger patient.

In 41 years of practice I have seen 6 fatal cases of agranulocytosis. Two were men aged 24 and 64 years. Four were women, the youngest being a schoolgirl of 15 and the oldest 71 years of age. During the same period I have seen 5 cases which proved not to be fatal. All had severe neutropenia associated with pyrexia and mucous membrane ulceration. Four were women and one was a male of whom the youngest was 17 years of age and the oldest 70. Five of the fatal cases were seen between 1924 and 1940. One fatal case, to be described in detail, was seen in 1963. Four of the non-fatal cases were seen between 1935 and 1940. One was seen in 1946. All of the patients were White. All except one had taken tablets containing amidopyrine.

I have seen 6 cases of neutropenia developing while the patient was under treatment for some other condition. One case was caused by sulphapyridine; one was attributed to Thiouracil; 2 cases were attributed to Novalgin (the offending amidopyrine has now been taken out of this useful tablet); and 2 cases were taking phenylbutazone (Butazolidine) for arthritis.

All these patients recovered when the offending medication was discontinued and did not develop agranulocytosis. These patients all complained of weakness and of vague pains. In all, the white-cell count was between 1,500 and 3,000/cu.mm. with a relative neutropenia. None of these patients suffered any permanent ill-effects.

A busy general practitioner, who has had the good fortune to be on the staff of a hospital for 40 years and who is frequently called in as a consultant, has the opportunity of seeing many interesting and unusual cases. To have seen 11 cases of agranulocytosis in this period suggests that it is not a very common condition, but I am satisfied that the incidence is higher than is suggested by available statistics and that in many cases a correct diagnosis is not made. The usual diagnosis 40 years ago was Ludwig's angina. In some cases the suspected diagnosis was diphtheria. Correct diagnosis depended then, as it does now, on a high index of suspicion, and the death certificate does not necessarily tell the full story. Not only must we have a high index of suspicion when dealing with the patient, but we also need a critical mind when we prescribe proprietary preparations.

The information given by trade representatives and purveyors of samples is no doubt the truth, but is not necessarily the whole truth. Potentially dangerous drugs can masquerade under innocent-sounding chemical names. The doctor must know what he prescribes—he is responsible.

There is no doubt that agranulocytosis is not as common as it used to be. This, in my opinion, is entirely due to the wide variety of analgesic preparations now available and to the fortunate reduction in popularity of amidopyrine-containing preparations. I have seen only one fatal case which could not be attributed to amidopyrine.

The most popular, and certainly the most effective, tablet dispensed both by doctor and chemist used to be Veramon. It stopped headache, backache and dysmenorrhoea. It could be obtained without prescription and was used both by schoolgirl and grandmother. It was a mixture of barbitone and amidopyrine and an identical tablet of South African manufacture was sold at a lower price under the name of Verosan. The same tablet is still available under the name of Ganol.

Pyramidon (the trade name of amidopyrine) used to be almost as popular as aspirin, particularly in Germany, but is no longer in general use in South Africa. Study of the available literature suggests that amidopyrine alone is not as dangerous as amidopyrine in combination with other drugs, and the most dangerous of all is a combination of amidopyrine and barbiturate. The drug is not always identified as a constituent of the tablet, because it can masquerade under different names. The BPC name is aminopyrine; the US National Formulary calls it amidopyrine and it is also known as aminophenazone, dimethyl aminophenazone and dimethyl amino antipyrine. It actually is 4 dimethyl amino 2:3, dimethyl-1-,phenyl pyrazole-5-one.

The first case of agranulocytosis that I diagnosed in my practice was seen in 1926. The patient was a village general practitioner aged 64 years. He was being treated by a friend and colleague for 'Vincent's angina'. He had complained of a sore throat for some weeks and had been provisionally diagnosed as diphtheria, but the laboratory found no evidence of diphtheria organisms, but reported the presence of Vincent organisms. When he failed to respond to Mandl's paint and phenol gargles, he was given frequent injections of Neosalvarsan and the throat was painted at regular intervals with the same arsenical solution.

After two weeks of this regimen, the temperature remained high, the pulse rapid and thready and the patient had entered the happy stage referred to in the old textbooks as 'low muttering delirium'. When I was asked to see him in consultation, the right tonsil, uvula and part of the soft palate had been replaced by a dirty greyish slough. The white-cell count was 400 cells/cu.mm. He died soon after I suggested that he be given no more arsenic.

The other 4 fatal cases seen before 1940 could all be attributed to Veramon. All had complained of general malaise for about a week. All had been in the habit of taking Veramon tablets for headache or dysmenorrhoea and all had taken Veramon during the 2 days preceding the onset of the acute illness. The onset in all cases was sudden. All complained of severe sore throat, severe headache and rapidly progressing weakness. The temperature varied between 102°F and 105°F. The pulse was rapid. All had necrotic lesions involving tonsillar fossa, uvula and soft palate. One had a necrotic lesion of the vulva. All had white-cell counts of 1,000/cu.mm. or less. No abnormality of the red-cell series was noted in any of these patients. All were given intravenous injections of sodium pentose nucleotide and all were dead within 5 days.

The patients with neutropenia, pyrexia and mucous membrane ulceration and who recovered had white-cell counts between 1,500 and 3,000/cu.mm. All except one had taken Veramon and the fifth had taken Sulphanilamide. Three were given intramuscular sodium pentose nucleotide (20 ml. daily). Two were given Aolan (filtered sterilized milk for intramuscular injection) and one of these was also given intravenous Electrargol, a once-popular silver preparation used in the treatment of septicaemia. The therapy used is now of historical interest only, but I was satisfied at the time that it was life-saving.

The last case in the series is that of a woman of 71. She had a painful varicose ulcer. Otherwise her health had been good. About 5 weeks before her death the ulcer was very painful and I gave her a sample of a tablet, new at the time, called Orfenso. Orfenso, which is made in South Africa, according to a well-advertised Austrian formula, contains caffeine, paracetamol, amidopyrine, diphonal keto hexane and some other constituents. It was most effective and the patient assured me that she had never taken better tablets.

A week later she developed tonsillitis with a temperature of 102°F. This responded to Albamycin-T and within 3 days the temperature was normal, but her throat was still sore. She did not regain her normal strength for about 10 days. Her case record is as follows:

27.8.63—Given sample of Orfenso tablets for painful varicose ulcer with peripheral vascular spasm. Took 2 tablets daily for 3 days. Pharmacist was given permission to dispense an additional tube of tablets which were most effective in relieving the pain. Optulle (paraffin gauze) was used as a dressing for the ulcer.

3.9.63—I was called in on account of the temperature, general malaise and severe sore throat. Right tonsil was enlarged and there was a purulent exudate on the tonsil. Tonsillar glands were enlarged and tender. Albamycin-T, 250 mg. 4-hourly, was prescribed.

6.9.63—Temperature and pulse normal. Still complaining of sore throat, but general condition good.

10.9.63—Complaining of backache, pain in the limbs and loss of appetite. Temperature and pulse normal, urine normal. Given a vitamin tonic (Elixir B.G. Phos.).

17.9.63—Feeling very much better. Throat fully recovered. Advised to continue taking the tonic prescribed.

25.9.63—Complained of severe sore throat, backache, headache and pain in the limbs of sudden onset, but did not inform me that she was ill. Had taken 2 Orfenso tablets per day, on the 2 preceding days on account of the painful varicose ulcer.

26.9.63—Seen at 6 p.m. Temperature 103°F; pulse 120 per minute; left tonsil and uvula were replaced by a greyish slough. There was an ulcer in the mouth. An ulcer was also noted in the ano-rectal mucosa. She was immediately admitted to hospital.

Blood count: haemoglobin 95%. Total leucocytes 650/cu.mm., polymorphs 15%, lymphocytes 85%. Red cells normal.

She was given: (*i*) Mysteclin V, (tetracycline with a fungicidal preparation, Mycostatin, Nystatin), 250 mg., 4-hourly; (*ii*) Prednisone, 10 mg. 4-hourly; (*iii*) Vitamin B_{12}, 1,000 mg.; and (*iv*) Prostaphlin A, 2 capsules 4-hourly.

27.9.63—Owing to difficulty in swallowing, oral medication was discontinued and she was given an intravenous drip

alternating dextrose saline and dextrose water with the addition of: 2 million units of penicillin, 40 units of ACTH, 100 mg. of hydrocortisone, and 100 mg. of ascorbic acid, per each vacolitre. She was given vitamin B_{12} and Penbritin intramuscularly.

28.9.63—The patient's condition was deteriorating. There was now a large slough in the anus, and large slough on the vulva and a rapidly increasing necrosis in the throat, mouth and pharynx.

Blood count was: haemoglobin 13·2 G/100 ml. (89%), leucocytes 350/cu.mm., neutrophils 14% and lymphocytes 86%. Red cells normal.

Owing to the deteriorating condition the patient was given 1,000 ml. of fresh blood.

29.9.63—The report on the blood culture sent off on 27.9.63 was positive for *Bacillus pyocyaneus*. Treatment was continued with increased dosage of ACTH, hydrocortisone, penbritin, ascorbic acid, vitamin B_{12} and a repeated blood transfusion. The nursing staff were given strict instructions to observe precautions to prevent the spread of the virulent organisms to other patients or wards.

The patient's condition continued to deteriorate. The sloughs became larger and there was some rectal haemorrhage after separation of a slough. Death took place on 4.10.63.

SUMMARY

Werner Schultz in 1922 described a rare disease characterized by sudden onset, severe and rapidly progressive necrotic lesions in the pharynx, marked reduction in the number of circulating neutrophils, profound toxaemia and death.

In 1931 Kracke attributed the increasing incidence of the disease to the increasing use of coal tar derivatives as therapeutic agents, and soon reports appeared incriminating amidopyrine as one of the drugs likely to cause this condition.

More than 450 drugs have been named as possible causes of blood dyscrasias, but amidopyrine, especially in combination with barbitone, is the most common cause of acute agranulocytosis. It is in all probability a disease caused by drug hypersensitivity. The reaction develops suddenly after 7 - 10 days' administration of the drug or occurs on the initiation of a further course of therapy.

Modern treatment with antibiotics, steroids, intravenous fluid and blood transfusions, has not materially improved the prognosis. With a total white-cell count of under 1,000/cu.mm. and polymorphs less than 20% death must be expected.

It is of interest that the erythrocyte count and haemoglobin level are not disturbed.

In over 40 years of busy practice I have seen 6 fatal cases, all but one caused by amidopyrine-containing compounds. I have also seen 5 cases of neutropenia with pyrexia and throat ulceration which did not develop into typical agranulocytosis. Four of these cases were attributed to Veramon (amidopyrine with barbitone) and one was attributed to Sulphanilamide. All of these patients recovered.

Amidopyrine compounds are again becoming popular. Those who prescribe them will have many satisfied patients, but may also, quite unexpectedly, have a death from fatal acute agranulocytosis. There can be no justification for the use of potentially dangerous drugs, which are never essential.

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