AGRANULOCYTOSIS AND AMIDOPYRINE*

BY

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Attention was first drawn to " agranulocytic angina " by Werner Schultz[1] in 1922. On the basis of five cases he outlined a hitherto unnoticed clinical syndrome consisting of the association of angina, in the sense of ulceration of the throat, with a diminution or disappearance from the blood of the white cells of the granular order. The syndrome is striking and not easily missed ; that it was something new in the clinical field is indicated by the fact that, although unnoticed before, from the time of its first description by Schultz cases have been recorded in increasingly large numbers.

America, Germany, and Denmark have provided by far the greater number of case reports ; in this country the condition has remained comparatively rare. The first case to be reported here appears to have been that of Batten[2] in 1929. Since that time some twenty further cases have been placed on record, bringing the total up to about twenty-five. A number have escaped recording ; Adams[3] points out that from 1930, when the condition first figures in the Registrar-General's report, up to 1934 eighty-two deaths were recorded as being due to agranulocytic angina. The annual mortality incidence increased from two in 1930 to thirty-nine in 1934 ; a certain number of these cases were, however, as Adams suggests, probably not true examples of the condition. Death from the condition first formed the subject of a coroner's inquiry in this country in November, 1935[4] ; two further inquiries into deaths from the same cause were held in 1935 and, so far as I can ascertain, four have been held in the course of the present year.

It was early noted that the condition tended to affect persons past the prime of life and females rather than males. Stellhorn and Amolsch[5] in 1931 drew attention to a further peculiarity of the condition—namely, its singular affinity for persons belonging to or in some way associated with the medical profession. Harkins[6] in the same year reported eight cases, and remarked that of the subjects one was a medical practitioner, one a medical student, and one a nurse.

Aetiology

In the search for the cause of agranulocytic angina we must then look for a factor satisfying four propositions:

1. That it first made its appearance as an entirely new syndrome about fifteen years ago.
2. That it occurs much more commonly in Germany, Denmark, and America than in this country.
3. That it shows a peculiar incidence as regards medical men and those associated with the medical profession.
4. That it affects almost entirely those past the prime of life, and females rather than males.

Kracke and Parker[7] and Madison and Squier[8] in 1934 independently sought for a factor common to the first three propositions, and independently found themselves facing the newer analgesic and hypnotic drugs placed on the market since the war, largely as the result of the activities of German chemists.

There is little striking difference between the racial and climatic conditions of America, Germany, and Denmark, in which agranulocytosis has shown its main incidence, on the one hand, and Great Britain, in which it remains a rarity, on the other ; the peculiar national distribution of the condition cannot therefore be attributed to racial or climatic differences. It must be due to some difference in national habit ; both Madison and Squier and Kracke and Parker believe this difference to be the fact that the newer analgesics and hypnotics have never enjoyed that popularity in this country that they do in America and the other countries mainly affected.

The factor determining the greater incidence of the condition on the medical rather than on the lay public might be supposed to be that of better and earlier diagnosis. Of this Kracke and Parker will have nothing, remarking that " it is well known that physicians are most negligent of their own health." On the whole, there appears to be truth in the observation.

From year's end to year's end the medical man is deluged with samples or offers of samples of new drugs. Most of these turn up in the form of attractive and easily ingested tablets, accompanied by readable fiction indicating their use and efficacy in the common ailments—rheumatic diseases, sleeplessness, headache, and so forth—which are the common lot of mankind as years advance. Naturally, it is on medical practitioners, or on those near and dear to them—wives, nurses, and so forth—that these samples are most widely tried.

Kracke and Parker and Madison and Squier independently searched among the newer drugs of wide distribution for the offending agent. Their search disclosed the fact that in a very large number of cases before the onset of the agranulocytic state the subjects had been taking amidopyrine in some form or other. This drug in various combinations, mainly with the barbiturates, appears in a vast number of proprietary tablets and under a multiplicity of names.

As the high incidence of agranulocytosis among those associated with the medical profession has been fallaciously attributed to earlier diagnosis, so the low incidence in this country has been attributed to failure in diagnosis. My own experience would lead me to disbelieve this. For the past ten years I have been on the watch for the condition, but did not meet it until about eighteen months ago. The differential diagnosis is not altogether easy: in the ten years I have seen altogether six cases showing diminution or absence of the granulocytes, which were at first diagnosed as agranulocytic angina. Of these, four occurred in children and two in young adults ; observation and post-mortem examination ultimately showed them all to be cases of lymphatic leukaemia without discharge of the abnormal cells into the blood stream—in other words, of " aleukaemic " leukaemia.

Illustrative Cases

In the past eighteen months I have seen three cases of agranulocytic angina, in all of which amidopyrine or an allied drug had been administered before the onset of symptoms. These cases are as follows:

CASE 1

A woman, aged 70, had been suffering from rheumatic pains ; for this she had been treated by her own doctor with veramon, of which preparation she had taken forty-three tablets in the course of ten weeks. The rheumatic pains were greatly benefited, but she developed an ulcer of the mouth with pyrexia, and the general condition failed to improve. When first seen by myself she was complaining of pain and dysphagia, the fauces were red and oedematous, and there were shallow ulcers upon the buccal mucous membrane and the tongue. Examination of the blood showed: haemoglobin, 50 per cent. ; red cells, 3,670,000 per c.mm. ; and white cells, 2,000 per c.mm. with complete absence of polymorphs. Pentnucleotide 10 c.cm. every six hours was ordered, but the patient failed to improve and died before

* Read in the Section of Pathology and Bacteriology at the Annual Meeting of the British Medical Association, Oxford, 1936.

more than 20 c.cm. had been administered. The post-mortem examination showed ulceration of the tongue and buccal mucous membrane and of the left vocal cord; the lower lobe of the right lung was solid.

CASE 2

A man, aged 52, suffered in 1933 from arthritis which was treated with novalgin. The dosage is uncertain, but several tablets had been taken at irregular intervals up to three times daily for some months until November, 1934, when he began to experience increasing lassitude and malaise, and to run a temperature. The tonsils were enlarged, and in January, 1935, he was admitted to a nursing home for tonsillectomy.

Examination of the blood showed: red cells, 5,280,000 per c.mm.; and white cells, 800 per c.mm. with only 5 per cent. of polymorphs. Tonsillectomy was postponed indefinitely. In the course of the succeeding week the patient was given a total dosage of 115 c.cm. of pentnucleotide without the slightest improvement in the blood picture. Towards the end of the course the patient showed rather alarming collapse after the injections, and on this account the treatment was stopped. For the next two weeks he received irradiation of the long bones without benefit.

During all this time the patient had been pyrexial. On one occasion he had a rigor; this was followed by the development of a small pustule upon the left arm. Examination of the exudate from this showed only a few lymphocytes and myriads of cocci which on culture proved to be *Staphylococcus albus*. The lesion healed in a few days. At this stage the patient was removed to his own home. The tonsils were still enlarged and ulcerated and he had completely lost his voice. About two weeks later he complained of pain in the right chest and developed a pleural rub and cough. Later there was copious sputum which appeared to be purulent, but which on microscopy showed only mucus and myriads of organisms with complete absence of pus cells. During all this time the fever had persisted. Towards the end of March, 1935, some three months after the diagnosis of the agranulocytic state, the temperature for no apparent reason fell, and a blood film showed 55 per cent. of polymorphs; sputum taken a few days later showed numerous pus cells. It was evident that the agranulocytic state had come to an end. From this time onwards recovery was uneventful; when last seen at the end of 1935, the patient stated that he had never felt better in his life. This case has been reported by Johnson.[9]

CASE 3

A woman, aged 46, was admitted to the Royal Hospital under the care of Dr. J. H. Sheldon on September 27th, 1935, with a four-months history of diffuse cutaneous oedema, dyspnoea, and lassitude. On admission she had some thickening with erythema and oedema of the skin of the face, neck, and shoulders; the erythematous areas showed pigmentation which later became more marked. There was peripheral neuritis in both legs. The blood contained: haemoglobin, 62 per cent.; red cells, 3,840,000 per c.mm.; white cells, 7,300 per c.mm. with 72 per cent. of polymorphs. The condition was tentatively diagnosed as "dermatoneuromyositis," and treatment with vitamin concentrates was initiated. On vitamin B the patient was showing considerable improvement.

On November 11th allonal up to two tablets daily was prescribed, and from this time until her death the patient took about 125 tablets of the drug. On December 23rd she complained of sore throat; at first there was only some oedema and reddening, and in spite of it the general condition continued to improve. About the middle of January, 1936, ulceration developed, and the temperature rose and persisted from then onwards. Examination of the blood on December 31st showed only 1,300 white cells with complete absence of granulocytes. The ulceration of the throat spread, large sloughs developed, and the patient died on February 7th with persistence of the absolute agranulocytosis. The post-mortem examination revealed severe ulceration of the buccal mucous membrane, the fauces, and the larynx. The bone marrow of the femur was gelatinous and oedematous, but, as in Case 1, a microscopical examination showed no evidence of myeloid hypoplasia.

Case 2 above throws an interesting light on the treatment by pentnucleotide, from which at one time great things were hoped. The dosage in this case was ample and continued, but without the slightest effect upon the agranulocytosis. Two months later the patient made a spontaneous recovery for which no credit for the pentnucleotide can be claimed. Other observers, notably Plum,[10] have remarked similar failure on the part of the blood to respond to pentnucleotide in cases of agranulocytosis following on the use of amidopyrine or its allies.

Sensitivity to Amidopyrine

The evidence that amidopyrine and its close allies are capable of causing agranulocytosis appears to be overwhelming. The case is, however, by no means straightforward. Not everyone taking the drug is affected, and attempts to bring about the condition in experimental animals by the administration of amidopyrine have given no significant results. Experimental work on human subjects not known to be sensitive to the drug has so far been equally unfruitful. Schilling[11] gave amidopyrine, both with and without barbiturates, to a large series of hospital patients of both sexes and all ages without producing any change in the blood picture.

It is very evident that sensitivity to the drug is confined to certain individuals whom in the light of present knowledge we have no means of identifying beforehand. This state of affairs resembles that found in the group of phenomena falling under the head of "allergy," and an attempt has been made to enmesh agranulocytosis in that far-reaching net. Unless, however, the term "allergy" is to be used merely as a cloak for ignorance there seems little justification for the attempt. Amidopyrine, it is true, shares with many other drugs the peculiarity of producing in certain individuals a skin rash; such rashes are usually regarded as "allergic." Both Plum and Schilling observed subjects who gave a skin rash after the ingestion of the drug, but neither found any change in the blood picture. Plum performed an intradermal test with a small dose of amidopyrine on a subject known to develop agranulocytosis after the ingestion of the drug, but obtained no skin reaction. This appears to offer conclusive evidence against the "allergic" theory.

The fact, then, is that to the vast majority of human subjects amidopyrine may be administered without harm, and possibly in certain circumstances even with benefit. From time to time, however, a person is encountered who after taking the drug develops a state of agranulocytosis. Such subjects are almost always, possibly always, past the prime of life, and are more commonly women than men.

The Sex Hormone Factor

In view of this experience it is difficult to avoid the conclusion that sensitivity to the drug is in some way associated with a change in the nature or balance of the sex hormones. The "change of life" has in the past been regarded as the prerogative of the female of the species. Evidence is accumulating that profound hormonal changes usher in the end of active sexual life in man as well as woman, and that the changes are to some extent similar in the two sexes.

Most workers who are in the habit of performing large numbers of routine examinations of blood pictures recognize that a relative leucopenia with diminution of the granulocytes is by no means an uncommon finding in women past the menopause; the case reported by Jackson and Merrill,[12] in which the question of amidopyrine does not arise, points very clearly to a relation between the sex hormones and agranulocytosis. The

subject was a woman, aged 30, who during a period of observation of one year was found to develop a condition of agranulocytosis at each menstrual period. Pentnucleotide was without notable effect, but the patient responded well to injections of antuitrin-S. Later she refused treatment, and died as a result of a phlegmon of the buttock. In this connexion it is noteworthy that of Plum's eight patients treated by pentnucleotide, blood transfusion, and in other ways, all died except one who was treated with folliculin.

No evidence is as yet to hand in regard to the metabolism of the sex hormones in sufferers from agranulocytosis, and in the nature of things it must be long before it can accumulate ; at present treatment with sex hormones, though justifiable, must be regarded as empirical.

Pathogenesis

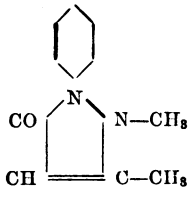
The mechanism of production of agranulocytosis remains obscure. The rapid diminution of the white cells in the circulating blood after the administration of a test dose of amidopyrine to a sensitive individual is striking ; Madison and Squier as well as Plum found a marked fall within from two to four hours. The obvious explanation of this rapid disappearance is a destruction of the cells in the blood ; examination of the blood, however, fails to reveal any damaged cells or other evidence of their destruction. Beck[13] has suggested an arrest in the process of maturation of the cells in the bone marrow, but it is difficult to see how a mere arrest of maturation could bring about so sudden a fall in the circulating leucocytes. The work of Weiskotten,[14] and of Roberts and Kracke,[15] would seem to establish the life of a leucocyte as being at least four days ; a mere arrest of maturation could hardly produce the rapid fall in white cells demonstrated by Plum and Madison and Squier. Such knowledge of the state of the bone marrow as exists at the moment throws little light on the matter. According to Beck, two types of bone marrow may be found in agranulocytosis—one showing degeneration and myeloid aplasia and the other myeloid hyperplasia. It is on the occurrence of these latter cases, as reported by Fitzhugh and Krumbhaar[16] and by Rosenthal,[17] that the theory of maturation arrest is largely based. In my own two cases which came to necropsy the bone marrow of the femur was gelatinous and oedematous, but showed no lack of cells of the myeloid order. Degenerative and post-mortem change made it impossible to ascertain whether primitive cells were present in greater or lesser numbers than normal ; the general impression was that of a moderately active, and certainly not of a hypoplastic, bone marrow.

Pentnucleotide was introduced as a means of stimulating maturation of the leucocytes, and in normal subjects it seems to be effective in this respect. As pointed out above, the evidence goes to show that in agranulocytosis following on the use of amidopyrine it is ineffective. Destruction of white cells in the circulation, cessation of function on the part of the bone marrow, and maturation arrest of the leucocytes do not seem satisfactorily to fit the observed facts ; we remain in the dark as to the intimate nature of the mechanism of the production of agranulocytosis.

Why amidopyrine and one or two near neighbours should produce agranulocytosis remains obscure. Amidopyrine is a coal-tar derivative, and contains a benzene ring. Selling[18] a quarter of a century ago drew attention to the effect of benzol itself in causing a diminution of the white cells ; its behaviour, however, is entirely different from that of amidopyrine. Benzol is a universal bone marrow poison ; its action is not confined to a few susceptible individuals as in the case of amidopyrine. Many cases of agranulocytosis following on exposure to benzol and the exhibition of drugs such as arsphenamine, dinitrophenol, and so forth, containing a benzene ring have been reported, and there has been a tendency to implicate the benzene ring in amidopyrine as the cause of its peculiar action on the bone marrow.

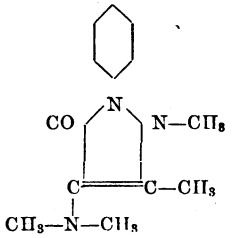
Kracke and Parker have developed this thesis in considerable detail. They point out that only drugs comprising a benzene ring with a substituted amino (NH_2) group have been implicated as causing agranulocytosis. Aspirin, which though comprising a benzene ring is without this substituted group, has never been blamed. This group of primary substituted amines they refer to as the " benzamine " group ; in it are included such widely used drugs as phenacetin and acetanilide. Kracke and Parker are inclined to regard these as suspect. Phenacetin, however, has been widely used in this country for over a quarter of a century, and it is difficult to believe that, had it been culpable, its action should so long have escaped detection. The same applies in a lesser degree to acetanilide.

The more case reports become available the more is amidopyrine implicated as the most common initiator of agranulocytosis. Amidopyrine is a derivative of antipyrine, which consists of a benzene ring with a pyrazolone ring attached.



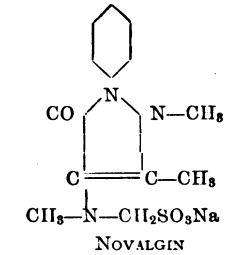
ANTIPYRINE

In amidopyrine the H of one of the methyl groups is replaced by the radical $N(CH_3)_2$.



AMIDOPYRINE

Novalgin resembles amidopyrine, except that in this case substitution is by the radical $CH_3—N—CH_2SO_3Na$.



NOVALGIN

Dr. F. Roche Lynch has suggested (personal communication) that this substitution in the pyrazolone ring may be the factor responsible for the production of agranulocytosis.

Summary and Conclusions

The ingestion of amidopyrine and of its close allies containing a benzene and a substituted pyrazolone ring is capable in sensitive subjects of giving rise to agranulocytosis.

These drugs exert their peculiar action only on subjects, either male or female, who have passed the "change of life."

Susceptibility to this action is probably associated with an alteration in the nature or balance of the sex hormones.

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ALKALI POISONING

A DANGER IN THE TREATMENT OF GASTRIC ULCER

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During the past few years several drugs which have been employed without suspicion of seriously harmful effects have been discovered to produce profound toxic disturbances in certain susceptible individuals. Among such drugs prominence has been given to the dangers of dinitrophenol, and more recently to those of amidopyrine. Dinitrophenol was for a time recommended for reducing weight in cases of obesity, but its use had to be given up because it was liable to cause cataracts, peripheral neuritis, liver damage, and other undesirable effects. Amidopyrine has long been a constituent of many sedative and analgesic powders, but has been found to cause in some people a dangerous toxic state associated with a serious fall in the number of polymorphonuclear leucocytes in the blood. The fact that this drug has been easily accessible to the public without medical prescription, and was indeed a constituent of some proprietary remedies, has increased its dangers, and a number of cases of death from its use have appeared in the coroners' courts.

It is the purpose of the present article to call attention to the occasional toxic effects of yet another common type of substance which is widely used without medical prescription. This is the group of alkaline powders which, in various mixtures, are prescribed and sold as "stomach powders" for the relief of gastric ulcer and other similar gastric complaints.

It may be considered remarkable, in view of the extremely widespread use of these alkaline powders, that reports of untoward effects have not been published more frequently. Two reasons are probably responsible for this. The first is the relative infrequency of susceptible subjects, and the second the peculiarly insidious nature of the symptoms, which may render the recognition of alkali poisoning difficult to those not well acquainted with the condition. But the recognition of alkali poisoning in the treatment of gastric ulcer is by no means new. Discussions of the subject have from time to time appeared in medical literature. As long ago as 1923 Hardt and Rivers in America reported a series of cases in which toxic symptoms developed during the routine treatment of gastric ulcer by the Sippy method, which includes the ingestion of alkalis. They were able to show that the sensitive individuals reacted biochemically in a different manner from the normal to the ingested alkali.

But until relatively recently the condition does not appear to have been well recognized in England. Indeed, in 1928 MacLean definitely denied that alkali ingestion, in the quantities recommended by him at least, ever led to the development of serious undesirable symptoms. And this pronouncement by MacLean probably went far to encourage the belief that alkali administration was as harmless in *all* individuals as it still appears to be in the great majority.

But there is now no doubt that a small group of persons does exist who are abnormally sensitive to some constituent of the alkaline powders. Cases of alkali poisoning do from time to time occur among patients under treatment in hospital, and a certain number are also admitted to hospital with toxic symptoms which have developed at home. It is because the histories given by the latter group often show clearly that the toxic condition was not recognized as such by their medical attendant that the present attempt is made to define more adequately the symptoms and signs by which such poisoning may be detected. The nature of the symptoms in these cases is often such that chronic alkali poisoning may persist for several weeks without the nature of the condition being appreciated unless the possibility of it is definitely borne in mind.

Symptoms of Alkali Poisoning

The condition develops typically in sufferers from gastric ulcer or other similar gastric disorder who are taking one of the usual alkaline mixtures for their complaint. These powders generally contain varying proportions of sodium bicarbonate, calcium carbonate, magnesium oxide or carbonate, and bismuth oxycarbonate. Whether one of these constituents is more likely to cause toxic symptoms than the remainder has not yet been determined. Occasionally it can result from other causes, and we have seen one case in which typical symptoms resulted from large doses of potassium citrate during the treatment of a pyelitis.

The mode of onset is nearly always insidious, but may be fairly rapid, reaching serious intensity in a day or two, or it may be much more chronic, developing progressively over a period of several weeks. It is the latter type of case which in general practice is most likely to be missed.

The relation to the amount of alkali taken is also variable. In very sensitive individuals it may come on within a few days of commencing alkali therapy, in others it may develop relatively rapidly in a person who has been taking alkalis without apparent ill effects for years. In the latter type of case it is not infrequently provoked by an increase in the alkali dosage.

During the early stages of the development of symptoms of alkali poisoning a marked deterioration in appetite is frequent. It appears to be directed against all types of foodstuff, but Cooke has noted a special antipathy to the taking of milk. This anorexia is frequently associated with attacks of vomiting of moderate severity. This vomiting is not necessarily associated with epigastric pain, which may be completely absent at the time. Nor is it of the severity and insistence encountered in pyloric obstruction, unless, of course, as may occasionally happen,