TREATMENT IN GENERAL PRACTICE

This article is one of a series on the management of some diseases of the blood and blood-forming organs met with in general practice.

PROPHYLAXIS AND TREATMENT OF AGRANULOCYTOSIS

BY

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During the last year agranulocytosis has aroused much interest in this country, an interest which some have felt to be disproportionate to its frequency. The disease is admittedly rare, but there has been a considerable increase in the number of cases reported, and it is certainly not so rare now as it was believed to be a few years ago. At a meeting of the Royal Society of Medicine in December, 1935, some twenty unpublished cases were mentioned by the speakers, and a succession of inquests reported in the lay press shows that the disease is not excessively uncommon and that it is giving rise to a good deal of apprehension.

Although cases of putrid sore throat, which were probably identical with agranulocytosis, were described last century the syndrome was rarely seen before 1922, when Schultz recorded a series of cases in Germany. A wave of almost epidemic proportion subsequently appeared in America, and the disease was responsible for more than 1,500 deaths in the United States in the three-year period ended in 1934. A little later Dutch and Scandinavian physicians observed a considerable number of cases, and finally there has been the outbreak in this country. In America and in the Scandinavian countries agranulocytosis is now subsiding as a result of prophylactic measures.

Signs and Symptoms

No age or sex is spared, but the highest incidence is in middle-aged women; there is sometimes a familial tendency. The symptoms are fever, profound prostration, and necrotic inflammation of the mucous membranes. Ulcerative pharyngitis is the usual local lesion, whence the name agranulocytic angina, but there may be membranous inflammation of the oesophagus, intestine, rectum, or vagina, or the patient may die without any gross mucosal lesion. The duration of the acute attack is from three to ten days, and the mortality is about 75 per cent.

The cardinal feature of the disease is a profound leucopenia; the total white count is rarely above 2,500 per c.mm., mainly due to a decrease of polymorphonuclear cells, which sink to a few hundreds and may completely disappear. There is no anaemia or haemorrhagic tendency in true agranulocytosis. Much the same clinical picture of leucopenia and necrotic inflammation may be present in leukaemia, aplastic anaemia, and certain toxicoses such as neo-arsphenamine poisoning, but the presence of anaemia and the shortage of blood platelets distinguish these conditions from agranulocytosis. The bone marrow in agranulocytosis is of normal extent and cellularity, and the erythropoietic tissue and megakaryocytes are normal. There is, however, a great diminution in the granular cells—polymorphonuclears and myelocytes—and in the late stages of the disease the leucopoietic tissue may become frankly atrophic.

Pathogenesis

It was first believed that agranulocytosis was the result of some peculiar infection which wiped out the cellular

defences of the body, but this view became untenable when it was discovered that leucopenia might precede by long periods any sign of infection. There is now no doubt that leucopenia is the primary factor in the disease, and that the patient succumbs to infection because of the shortage of leucocytes and the consequent defenceless state of the body. Later it was noted that attacks might recur at the menstrual periods and that the patients had often suffered from neuralgia or rheumatism, so that vague hormonal or toxic factors were suggested. Neither of these factors satisfactorily explained the undue frequency of the disease in medical people and their families, and in nurses. Finally came the discovery by Kracke in 1931 that the majority of those affected had used drugs of the coal-tar series, which was soon followed by the definite incrimination of amidopyrine (pyramidon). Of 172 cases of agranulocytosis attributed to drugs 153 followed the use of amidopyrine, six dinitrophenol, four neostibosan, two antipyrine, one aspirin, and one quinine.

Barbiturates are often combined with amidopyrine, but there is no evidence that the barbiturates alone have ever produced agranulocytosis. The explanation of the association of agranulocytosis with menstruation, rheumatism, and dental infection is that amidopyrine is used for the relief of the pain, while the medical profession suffers from its tendency to use new drugs, especially the much-advertised analgesics compounded of amidopyrine and a barbiturate, of which so many free samples are distributed.

Drug Aetiology

At first the drug theory of the aetiology of agranulocytosis was hotly contested, but time has shown that when careful histories are taken evidence of the use of amidopyrine is obtained in the great majority of cases. A vast array of proprietary preparations, from vitamin foods to influenza cures, contain amidopyrine. Unless leading questions are put the use of amidopyrine will not be discovered,* and even then it may be missed, as in some astonishing cases mentioned by Plum (1935). The evidence incriminating amidopyrine as the chief cause of agranulocytosis may be classified as circumstantial, experimental, and direct.

The circumstantial evidence is that the majority of patients with agranulocytosis have taken amidopyrine, and that the rise and fall of its incidence in a hospital or country run parallel to the introduction and abandonment of amidopyrine. The present epidemic prevalence of the disease is probably attributable to two main causes: first, the fashion of using amidopyrine instead of salicylates in the treatment of rheumatism and arthritis; and, secondly, the flooding of the market with analgesics based on Pfeiffer's compound of a barbiturate nucleus with amidopyrine. The experimental evidence is that, although the complete syndrome of agranulocytosis has not been produced in animals, the ability to develop a leucocytosis is depressed by the administration of amidopyrine. Direct proof of the culpability of amidopyrine has been obtained by observing the effect of a test dose on the white blood count of patients who have suffered from agranulocytosis. The number of white cells falls abruptly within a few hours, and it may be

* This article was written before details were available of the Poisons List Confirmation Order, 1935, which came into force on May 1st, 1936, and according to which amidopyrine can now be supplied only upon a written order.

several days before it returns to normal. At the same time the patient may complain of general symptoms such as malaise, sore throat, and pyrexia.

Amidopyrine

As I have already indicated, all cases of agranulocytosis are not due to amidopyrine, nor can it be assumed, just because a patient has taken this drug, that a subsequent attack of agranulocytosis is necessarily due to amidopyrine. A number of patients have taken amidopyrine throughout an attack of agranulocytic angina and have recovered, and others have taken massive doses without effect. Rigorous proof would demand the demonstration of sensitivity to amidopyrine in every case before the illness is accepted as due to it.

In spite of these reservations we must regard amidopyrine as the chief cause of agranulocytosis. It must also be emphasized that, just as a paroxysm of asthma in an aspirin-sensitive asthmatic is entirely different from the effect of an overdose of aspirin in an ordinary subject, so the symptoms of agranulocytosis are quite different from the usual toxic effects of an overdose of amidopyrine. There is no reason to expect cyanosis, skin eruptions, discoloration of the urine, or accumulation of amidopyrine in the tissues from the small amount of the drug which will provoke an attack of agranulocytosis in the sensitized individual.

It would be interesting to discuss the "epidemic constitution" of agranulocytosis, as it is unlikely that amidopyrine is the only factor involved. It would also be interesting to inquire into the mechanism of the sudden disappearance of the white cells on the ingestion of amidopyrine by the sensitized subject. But a more pressing problem is the attitude that we as practising physicians are to adopt to the prescription of this drug.

Therapeutic Considerations

No one would think of banning the use of aspirin just because 10 per cent. of asthmatics are sensitive to it; we merely exercise special care in prescribing aspirin to asthmatics. On the other hand, dinitrophenol is so dangerous, and its value so problematic, that many of us think its therapeutic use should be abandoned. Some people are abnormally susceptible to the toxic action of atophan, which is not only a non-specific analgesic but also the best remedy for gout; most of us have concluded that atophan should be used only in gout, and then with caution and supervision.

What is the position of amidopyrine? There is an impression that in certain cases of migraine and neuralgia amidopyrine is superior to other analgesics, and that it could ill be spared. The whole question of the relative value of drugs such as aspirin, acetanilide, phenacetin, phenazone, and amidopyrine, and their potentiation by caffeine derivatives, barbiturates, and opiates has been left in the biased hands of the manufacturing chemist. A careful clinical analysis would certainly be as helpful, and might condemn the new-fangled remedies just as strongly, as Hoyle and Evans's work on angina pectoris or Garrod's work on urinary antiseptics. At present, to suggest giving up amidopyrine completely would arouse a storm of protest. Amidopyrine is a dangerous drug, and all remedies which contain it (their name is legion) should be clearly branded as dangerous drugs, with the word amidopyrine, and not with some alias such as dimethyl-aminophenyl-dimethyl-pyrazolon. Amidopyrine should not be used as an influenza cure, a febrifuge, or a banal analgesic, but should be reserved for cases of severe pain which have resisted other remedies.

The majority of wage-earners in this country obtain their medicine under the national health insurance scheme

or from a hospital, and are only able to receive it by regular attendance on their doctor. I see no reason why other members of the community should be allowed to use powerful remedies such as amidopyrine or a barbiturate without the same regular medical supervision.

Sensitization

The consumption of amidopyrine is measured in tons, and it is obvious that only a small percentage of the population has an idiosyncrasy to the drug. How can we distinguish those likely to be susceptible? How long does it take for sensitization to be acquired? How much amidopyrine is necessary to sensitize a patient? Is there any warning of the development of sensitization? How long does sensitization last? These are the questions we are likely to be asked, and it is not easy to answer all of them satisfactorily.

1. There is no means of distinguishing those likely to become susceptible. Skin tests are unreliable, nor is it of much value to observe the effect of a single test dose on the white cells—the reaction will not be positive until the patient has become sensitized.

2. Cases are described by Fitz-Hugh (1934) in which the patient had used amidopyrine for only two or three days before the onset of agranulocytosis; it is, of course, difficult to exclude the previous taking of amidopyrine. At the other extreme are those patients who have taken amidopyrine for several years before the onset of agranulocytosis; on closer scrutiny of these cases it is found that only small amounts have been ingested at intervals, perhaps 5 or 10 grains every three or four weeks for migraine or dysmenorrhoea.

3. A total of between 1 and 2 grams has been sufficient to sensitize some patients. The total amount commonly ingested before sensitization develops is from 2.5 to 25 grams. When a patient has taken a total of 50 grams of amidopyrine with impunity (in divided doses, of course) it becomes progressively less likely that he will become sensitive, but there can be no absolute surety of safety.

4. It is probable that leucopenia always precedes the onset of acute symptoms, and the blood should be examined at regular intervals when amidopyrine is prescribed. Patients with extreme leucopenia may complain of lack of vitality, undue fatigue, stomatitis, and muscular pains, and watch should be kept for these symptoms. The time between the onset of leucopenia and the onset of acute illness is probably very variable, and depends on the chances of exposure to infection.

5. After an attack of agranulocytosis it may be six months or a year before the white count is stabilized at a normal level. It is probably longer still before the bone marrow regains its full powers of response to infection. The duration of susceptibility to amidopyrine is unknown, but it is a matter of years, and may be life-long.

6. So long as the patient is susceptible as little as 3 grains (0.2 gram) of amidopyrine may precipitate an acute attack of agranulocytosis.

Local Treatment

Prognosis and treatment of agranulocytic angina should be guided by daily white counts and examination of the stained smears for signs of renewed production of leucocytes. The earlier active treatment is begun the better the prognosis. All synthetic drugs of the types mentioned are forbidden. For the mouth and throat the regime recommended by Marriott (1934) may be followed:

"Every two hours when the patient is awake, and at least every four hours if asleep: (1) The mouth is thoroughly sprayed in every part of it with a 1 in 2,000 solution of percaïne in glycerin, about half an ounce to an ounce of the solution being used. This renders the mucous membrane sufficiently anaesthetic for the patient to tolerate vigorous swabbing. (2) Advantage is taken of the oral anaesthesia for the patient to be fed, and whatever form of liquid nourishment has been ordered is now given. (3) Every part of the mouth is thoroughly swabbed with a 50 per cent. solution of hydrogen peroxide, and then re-swabbed again just as

thoroughly with citric acid solution, 10 grains to an ounce of water. Soft swabs held in forceps should be used, and every corner of the mouth must be reached. (4) The mouth is irrigated with a pint of eusol solution, one part to three parts of water. The irrigation is carried out by means of a catheter attached to a douche-can or by the use of a Higginson syringe."

This regime errs, perhaps, on the side of over-thoroughness; it is important not to wear the patient out by "constant therapeutic nudging." Abscesses and areas of cellulitis should be drained, but only essential surgery should be done.

General Treatment

In this disease, as in pneumonia, the general care and nursing are the most important elements in treatment. Special remedies available are pentnucleotide, transfusion, liver extract, arsphenamine, and x rays. It is doubtful whether any of them has a specific action on the disease. Pentnucleotide is put up in solution in 10 c.cm. ampoules and is given by intramuscular injection. In the acute stages 40 to 50 c.cm. a day should be injected in divided doses. Little improvement can be expected until between the third and fifth days, hence the importance of beginning treatment early. Sometimes there are severe reactions to the drug—respiratory distress, abdominal pain, rigors, fever, nervous phenomena. If such reactions occur pentnucleotide may be given intravenously by continuous drip: 20 c.cm. of pentnucleotide is diluted in 1,000 c.cm. of normal saline solution, and the injection is given at a rate not exceeding 50 to 100 drops a minute. Undiluted pentnucleotide should not be administered intravenously. Treatment with 40 to 50 c.cm. a day is continued until there is a rise in the white count, and pentnucleotide is then given in smaller amounts until the white count has been normal for several days.

My own opinion is that transfusion is not indicated, but there are those who think it of value. It is suggested that the donor may receive an injection of 2 to 4 c.cm. of 5 per cent. nuclein, or 20 c.cm. of 10 per cent. saline, two or three hours before the blood is withdrawn to increase the leucocytes and the bactericidal power of the blood. Whether the donor is so prepared or not, a transfusion of 500 c.cm. of blood is given, and if well tolerated may be repeated once or twice at intervals of twenty-four to forty-eight hours. The value of liver treatment is dubious, but at any rate it is harmless. Liver extract is given by intramuscular injection, 4 to 8 c.cm. a day, until the patient is well on the way to recovery. A single intravenous injection of 0.3 gram of neo-arsphenamine may be given in the hope of stimulating the production of white cells and also of clearing up the inflammation of the mouth and fauces. Stimulating doses of x rays can only be administered by an expert, and are not without danger.

Treatment of Chronic Cases

In the chronic cases where there is leucopenia but no fever or infection a ten-day course of pentnucleotide, 20 c.cm. intramuscularly daily, may be given once a month until the white count is stabilized at a normal level. A long holiday by the sea or in the mountains, away from crowded centres of infection, is the ideal prescription. Where this cannot be procured the effects of ultra-violet irradiation may be tried. The diet should be rich in vitamins and in purine foods. Teeth may be scaled and cleaned, nasal sinuses treated by postural drainage, and pyelitis treated by mandelic acid; but dental extractions and the radical extirpation of septic foci should be postponed until the white count is stabilized at a normal level.

Nova et Vetera

JOHN OF MIRFIELD

John of Mirfield died in 1407. He came of a Yorkshire family and lived in London, where he had lands and shops. He was in Orders, and had some connexion both with the Priory and with the Hospital of St. Bartholomew in Smithfield. He wrote two voluminous works—the one called the *Brevarium Bartholomei*, the other the *Florarium Bartholomei*. The *Brevarium* is a compendium for those too poor to buy the large number of medical books in manuscript then necessary for the preservation of bodily health and to prevent such persons from falling into the hands of avaricious physicians. The *Florarium*, in like manner, is a guide to the attainment of spiritual health, and to prevent mankind from falling into the snares of the evil one. Neither work contains much that is original, but both are valuable as showing the methods of treatment and the mode of thought in England during the fourteenth century. Mirfield's manuscripts had already attracted the attention of Mr. A. J. Horwood, Mr. J. G. Mowat, and Sir Norman Moore. It has been left to a scholarly physician, Sir Percival Horton-Smith Hartley, and to Mr. H. R. Aldridge, assistant keeper in the Department of Manuscripts, to publish a critical account of the author and to give, with a translation, selected passages from his writings.¹ The result is admirable, for endless trouble has been taken to obtain facts hitherto unknown and to correct errors which have crept into the various manuscripts. Sir Percival, with his expert knowledge, has thrown much light on the chapter dealing with consumption, "De Ptisi," whilst both collaborators, by their wide reading, have supplied a running commentary in notes which are of very great value in elucidating the text. The dedication in elegant Latin is a worthy tribute to their classical knowledge. The book also contains three plates illustrating the early fifteenth century hand in which the manuscript is written, and a fourth, the facsimile of the entry relating to John of Mirfield's nuncupatory will.

The authors have produced a most satisfactory piece of work, which, in spite of its learning, is easy and interesting to read. It is a matter of common knowledge that the cathedral libraries, the College libraries of Oxford and Cambridge, and the great public libraries of the Kingdom contain a large number of medical treatises in manuscript. It would be a work of piety if men of leisure would follow the good example of Sir Percival Hartley and edit some of them, for they often contain much that is good but forgotten.

¹ *Johannes de Mirfield of St. Bartholomew's, Smithfield: His Life and Works.* By Sir Percival Horton-Smith Hartley, C.V.O., M.A., M.D., F.R.C.P., and Harold Richard Aldridge, M.A. Cambridge: At the University Press. 1936. (Pp. 191; 15s. net.)

It is proposed to hold the Annual Conference for Medical Officers in Industry Overseas on Thursday, July 16th, at the London School of Hygiene and Tropical Medicine, in order that medical officers in industry on leave from the Tropics may be able to meet their colleagues and discuss their problems. The main subject for discussion will be the prevention of disease—for example, the control of malaria and epidemic diseases in the Tropics—water supplies, sewage and refuse disposal, housing, the keeping of records, and hygiene generally. Medical officers practising on plantations, mines, railways, hydro-electric and construction schemes, and development companies generally are invited to attend. Government health officers will also be welcome. Applications should be made as early as possible to the organizing secretary, Ross Institute of Tropical Hygiene, London School of Hygiene and Tropical Medicine, Keppel Street (Gower Street), London, W.C.1.