such drugs, and when provided with evidence does so: but there is a lamentable lack of contact between clinical pathologists and the Poisons Board. I believe that there is a need for a small standing committee of clinical and forensic pathologists, whose terms of reference should be: "To collect evidence on the production of injurious effects by drugs administered for therapeutic purposes; to deduce from this, and any other evidence available, whether the therapeutic value of any such drug is great enough to warrant its continued use; and to submit representations and recommendations to the Poisons Board on the regulations for the manufacture, sale, advertising, packaging, labelling, or prescription of drugs which have been shown to produce injurious effects."

The Association of Clinical Pathologists has many forensic pathologists as members; if the association formed a committee, evidence could be obtained without excessive formality, but the committee would have no official status. Alternatively, a committee could be set up by the Central Health Services Council, with the advantage of having statutory justification. Probably maximum efficiency would be attained if the A.C.P. set up a small committee to collect evidence, and if the Central Health Services Council also set up its committee, to which the members of that formed by the A.C.P. were co-opted.

In the specific case of amidopyrine it is clear that the present regulations for Schedule IV are inadequate. Various rules have been made in different countries, all of which would have some disadvantage in England. I suggest that the Poisons Board should introduce a new regulation to the effect that "no prescription for amidopyrine, its salts, or mixtures of these with any other substance shall be valid unless the prescriber states specifically on the prescription that amidopyrine is required." The prescription for, say, veropyron could then read "amidopyrine mixture, veropyron," or "amidopyrine-barbiturate mixture, veropyron." Such a rule would ensure that no practitioner could remain in ignorance of the danger of the mixture he was prescribing, but it would in no way interfere with his responsibility or his right to order any preparation which, in his opinion, was necessary for the patient; nor would it interfere with the existing proprietary mixtures.

Summary

A case of agranulocytosis caused by amidopyrine is described.

It is shown that the best available evidence suggests that if this drug is administered regularly to a series of patients agranulocytosis will occur in about 0.8%.

It causes agranulocytosis in Great Britain when an amidopyrine mixture is prescribed under a proprietary name by a practitioner who does not know that it contains amidopyrine.

It is shown that, among a population which can obtain amidopyrine freely, an annual incidence of agranulocytosis between 2 and 5 per million may occur, and that if its use is encouraged the incidence may increase many times.

Possible substitutes for amidopyrine in mixtures are suggested.

Attention is drawn to other drugs with undesirable side-reactions. It is suggested that a standing committee of clinical and forensic pathologists should collect evidence on drugs causing injurious side-effects and submit their conclusions to the Poisons Board.

It is suggested that no prescription for a mixture containing amidopyrine should be valid unless the word amidopyrine appears on the prescription.

I am indebted to my colleagues in other countries who have so kindly and precisely replied to my inquiries; their names are given in the text. Summaries of the restrictions under which amidopyrine is prescribed in Norway and Sweden were given

by the Norwegian and Swedish Ministries of Health, and Dr. Torben K. With obtained the Danish regulations for me. The Ministry of Health of the Czechoslovakian Republic and the Czechoslovak Medical Society enabled me to correspond with Dr. L. Cermák: to all these I am indebted. I have been greatly assisted by the directors and medical advisers of several pharmaceutical manufacturing houses who have obtained unpublished observations and placed them freely at my disposal, and spared no trouble to ensure that this review is as truthful as possible. It is with regret that, at their own request, I do not mention them by name.

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AGRANULOCYTOSIS SUCCESSFULLY TREATED WITH A.C.T.H.

BY

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The association of pharyngitis with leucopenia was first described in 1902 by Brown and Ophuls, and the name agranulocytosis was later given to the syndrome of severe sore throat, prostration, and extreme reduction or disappearance of granulocytes from the blood which might be followed by sepsis and death (Schultz, 1922). In 1931 Kracke noted that the disease might be caused by certain drugs, and soon afterwards amidopyrine (aminopyrine) was incriminated and the high mortality of the cases caused by this drug was noted (Madison and Squier, 1934). Of all the drugs capable of causing the condition amidopyrine remains still one of the chief offenders: Plum (1937) found it responsible for the large majority of cases in Denmark occurring at this time, reporting 267 cases in which agranulocytosis had followed administration of this drug. Kracke (1938) stated that approximately 80% of drug-induced agranulocytosis was caused by amidopyrine or one of its derivatives. Although many new drugs since then have been incriminated, amidopyrine still remains one of the commoner causes of acute drug-induced agranulocytosis.

Because of this danger of agranulocytosis, amidopyrine has fallen out of favour in this country, though it remains popular on the Continent because of its excellent analgesic properties. What we see now prescribed in its stead are a number of proprietary

compound tablets containing the drug, and new ones are still appearing. Most physicians are not organic chemists and do not always appreciate the dangers of even small amounts of the drug in a compound tablet. There is one further point worthy of note: by substitution of the sodium salt of methyl-sulphonic acid for one of the methyl groups attached to the amino-nitrogen—a chemical manœuvre called sulphonation which results in increased solubility—the drug in this country escapes appearing on any schedule of dangerous drugs and may be purchased across the counter without prescription.

Sodium phenyldimethylpyrazolon methylamino-methane sulphonate ("novalgin" in this country, dipyrone or "novaldin" in the United States), freed from restrictions, remains essentially the same chemical substance as amidopyrine and should in theory be equally dangerous. That it is so is suggested by the fact that of the cases reported by Blake *et al.* (1935), Donnison (1936), Das Gupta (1936), Klumpp (1937), Moloney and Vidoli (1943), and Kneidler (1946) only the last, a mild case in a haemophilic, lived. While the drug has been considered by all the above authors to be the cause of the condition, it may be argued that the evidence in each case is indirect only and that other factors might have played an important part. Benjamin and Biederman (1936), however, in a human volunteer known to be sensitive to amidopyrine, reproduced symptoms within eight hours of taking 10 gr. (0.65 g.) of novaldin, with a drop in white cells to 2,800 per c.mm. (P. 46%) after 24 hours, complete recovery taking place in 72 hours. The case report which follows pursued the same pattern.

Case History

A housewife aged 65 was admitted to hospital on November 23, 1951. She had had frequent frontal headaches for three to four years, and, as aspirin caused abdominal pain, she took acetanilide on such occasions over a period of two to three years. She remained in good general health and lost no weight. In the past three months she had taken novalgin tablets; the total amount is uncertain, but at least three bottles of 100 tablets were dispensed. Three weeks before admission a severe sore throat began which steadily became worse. She experienced difficulty in swallowing, cough, loss of voice, and increasing weakness. She became febrile. For the 36 hours before admission she was given a total of 4 g. of sulphadimidine. Her previous history was negative but for the fact that since childhood she had been regarded as anaemic.

On admission the patient was seen to be a pale, very ill old lady, drowsy, uncooperative, and occasionally delirious. There was extensive superficial ulceration of the pharynx and soft palate, with much oedema and stringy mucus. The tonsillar glands were enlarged. A few basal rales were heard. The pulse was regular, 100 a minute; the blood pressure 130/80; temperature 101° F. (38.3° C.). A blood count read: Hb, 58%; red cells, 2,300,000 per c.mm.; white cells, 1,400 per c.mm. (lymphocytes 87%, prolymphocytes 4%, monocytes 6%, Türk cells 3%. No polymorphs were present). A throat swab gave a heavy growth of haemolytic streptococci.

Treatment and Progress

Soluble penicillin, 300,000 units intramuscularly four-hourly, with penicillin lozenges, 50,000 units three-hourly, was started. On November 26 2 pints (1.14 litres) of fresh Rh-negative Group O blood was given, and on November 28 10 oz. (284 g.) of packed red cells. Later on the 28th the blood count read: Hb, 98% (14.5 g.); red cells, 4,880,000 per c.mm.; white cells, 2,700 (lymphocytes 94%, mono-

cytes 4%, degenerate polymorphs 2%). She was also given over this period ascorbic acid, 200 mg. thrice daily, pyridoxin, 200 mg. daily, and "betalin" (vitamin B) compound, 2 ml., all by the parenteral route, with ferrous sulphate tablets, 6 gr. (0.4 g.) thrice daily, by mouth. On December 2 folic acid, 10 mg. twice daily, was started.

The patient was isolated from the beginning, and mouth-washes and gargles were given; but she took fluids poorly and became steadily more dehydrated, uncooperative, and ill. Her temperature remained elevated between 99 and 101° F. (37.2 and 38.3° C.), and she became progressively weaker. On December 2 haemolytic streptococci had disappeared from the throat, to be replaced on the 5th by a penicillin-resistant streptomycin-sensitive strain of *Staph. aureus* with subsequent rise in temperature. Streptomycin was started, 1 g. intramuscularly twice daily, on December 6. A chest skiagram was normal. Blood cultures were sterile. For marrow biopsy reports see Table. On December 6 it was obvious there was no response to treatment, and at this stage, 13 days after admission to hospital and five weeks after the commencement of her sore throat, in view of the failure of marrow biopsies or blood counts to improve and

Report on Bone Marrow. Total Nuclear Count

	26/11/51	5/12/51 Day before A.C.T.H. Started	11/12/51	7/1/52
Segmented polymorphs	Nil	Nil	5	11
Non-segmented ..	"	"	16	12
Metamyelocytes ..	"	"	24	18
Myelocytes ..	1	3	21	16
Premyelocytes ..	3	2	8	3
Blast cells ..	7	8	2	2
Eosinophils ..	"	"	"	1
Eosinophilic myelocytes	"	"	"	1
Lymphocytes ..	36	63	12	8
Prolymphocytes ..	7	5	"	"
Monocytes ..	1	"	3	1
Plasma cells ..	10	"	"	"
Normoblasts:				
Late ..	5	2	"	4
Intermediate ..	19	12	7	18
Early ..	7	4	1	1
Proerythroblasts	2	1	"	2
Reticulum cells ..	2	"	"	"
Remarks ..	Complete depression of myeloid series	Depression of myeloid series; marrow appears more hypoplastic	Marked granulopoiesis	Normal film

Chart showing effect of A.C.T.H. on the white blood cells.

the steady deterioration in the patient's general condition, it seemed very unlikely that a natural remission would occur, so A.C.T.H. was started, 20 mg. six-hourly for six days, 20 mg. twice daily for two days, and 10 mg. twice daily for two days: a total of 620 mg. over the 10-day period from December 6 to 16.

Progress on A.C.T.H.

After 48 hours her general and local oral condition began to improve and her temperature became normal. The Chart shows the rapid rise in polymorph white cells to a peak of 23,600 on December 12, and marrow biopsy reports (see Table) were equally striking. The white-cell count then fell to normal and remained so. The mouth was completely healed by the twenty-first day of treatment. By the ninth day she was vastly improved mentally and was co-operative. All-round improvement therefore was seen to occur on the third day of treatment, when 200 mg. of A.C.T.H. had been administered, and from that time she never looked back.

Response to Novalgin

After a month, as the patient was perfectly well with an entirely normal blood count, it was decided to try the effect of two tablets—10 gr. (0.65 g.)—of novalgin. These were given at 9 a.m. on January 23, 1952. Four hours later she began to feel unwell. She developed a headache which gradually spread to all limbs and the rest of the body. Immediately after lunch she vomited and was nauseated for the rest of the day. She complained of a headache, frontal in position. Blood counts at this time showed no change, the white cells being 5,800 per c.mm. (neutrophils 3,190 or 55%). The next morning the temperature had risen to 102° F. (38.9° C.), her symptoms were more marked, and shivering attacks occurred. She was definitely ill and had no inclination for food. She looked sallow and puffy around the eyes. Her white-cell count at 10 a.m.—that is, 25 hours after taking the drug—had dropped to 3,600 (neutrophils 75%). The white-cell count, repeated that afternoon and evening, remained low, as it did all next day, polymorphs dropping to 1,680 (42% of 4,000 white cells). A marrow biopsy showed no significant change at this time. Six days after administration of the drug, although the white cells had risen to 8,000, the neutrophils varied from 29 to 44% of the total (1,800 to 3,520). Two compound 5-gr. (0.32-g.) acetanilide tablets (acetanilide 60%, caffeine citrate 9.5%, and sod. bicarb. 30.5%), a drug which she had previously taken, were subsequently given. No symptoms followed their administration, and there were no changes in her blood count.

It was considered unsafe to repeat the experiment with novalgin, for, although the blood count could not be said to be entirely conclusive, the rapid return of her previous symptoms with neutrophil depression was regarded as enough proof that novalgin was the drug responsible for her condition.

Discussion

There is no doubt that in this case A.C.T.H. prevented a fatality; the patient was, in spite of all treatment, a dying woman when the injections were started. There have been two other cases reported to date, with similar results.

1. The first case was of agranulocytosis caused by a compound sulphadiazine-sulphamezathine (sulphadiazine-sulphamerazine preparation (Caldwell *et al.*, 1950). Here, although fever was abating before administration of the drug, cortisone given intramuscularly appeared to cure the condition rapidly and effectively, the white cells rising from 975 per c.mm. (no neutrophils present) to 25,400 per c.mm. (88% neutrophils) on the sixth day of treatment. After withdrawing cortisone the white-cell count gradually fell to normal levels over a period of a fortnight. Occasional eosinophils appeared on the ninth day after treatment was stopped.

2. In the second case a male patient, giving hypersensitivity reactions to several substances, developed agranulo-

cytosis after a course of sulphadiazine with chloramphenicol (McMillin, 1951). The former drug was taken to be responsible. A.C.T.H. was started, when, in spite of routine therapy, the patient was *in extremis*, the total white-cell count was only 450 per c.mm. (neutrophils absent), and the marrow biopsy showed almost complete arrest of maturation of myeloid cells at the progranulocyte state. Response was almost identical with that seen in our own case. After 48 hours on A.C.T.H. a marrow biopsy showed early response, even mature polymorphs being seen. Nuclear differentiation had far outstripped cytoplasmic and granular differentiation; often metamyelocytes with immature blue cytoplasm and azurophil granules were seen. Ten days after treatment was stopped the marrow biopsy showed no sign of maturation defect.

Finch *et al.* (1951), in an investigation into the haematological findings in cases of rheumatoid arthritis treated with cortisone and A.C.T.H., found a significant polymorphonuclear leucocytosis in all patients during treatment, lymphopenia being inconstant and unsustainable. The beneficial effect in the two cases noted above and in our own was, however, much more dramatic and rapid than could be explained in this way, and is more likely to have been in the nature of a direct desensitizing action on the marrow itself, and possibly on the circulating neutrophil cells also. Witts (1936) states: "In some cases of idiosyncrasy, such as agranulocytosis from amidopyrine, a mechanism akin to anaphylaxis is present, an initial dose being necessary to sensitize the patient"; and, again, "it is not known how long amidopyrine sensitivity lasts, but certainly for years and possibly for life." Benjamin and Biederman (1936) think the condition is a hypersensitivity to the drug, "the haemopoietic system acting as the shock organ." There is therefore a rationale for the use of A.C.T.H. or cortisone, and though they may act only in some cases of acute drug-induced agranulocytosis there seems enough evidence to warrant their trial in conjunction with antibiotics, isolation from infection, and other general measures.

Summary

A case of agranulocytosis is reported; the evidence incriminates novalgin (sodium phenyldimethylpyrazolon methylaminomethane sulphonate; sodium amidopyrine sulphonate) as the causative drug.

Amidopyrine is well known to be capable of causing agranulocytosis; novalgin, though escaping Schedule 4, is shown to be also dangerous.

A.C.T.H. produced rapid improvement in the clinical and haematological picture. This improvement began on the third day of treatment and was complete in three weeks. This is the third reported case of drug-induced acute agranulocytosis responding to A.C.T.H. or cortisone.

Our thanks are due to Dr. H. W. Macintyre and his technical assistants for the numerous haematological investigations in this case.

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