should always be suspect unless both testicles can be palpated with certainty, but in the great majority a urethroscopy will reveal a normal verumontanum and render unnecessary any more extensive exploration. Diagnosis without laparotomy may also be possible where the combination of anatomy and endocrine disorder points to the hormonal type of intersex female. The accompanying table sets out the common findings in the other types described in this paper.

The most difficult problem is provided by the newborn infant whose genitalia are of equivocal sexuality; the anatomy of the genital passages of all three main groups may be identical and, except in the cortin-deficiency cases, adrenal abnormalities may not at this stage be manifest. The urethral orifice is fortunately wide enough to admit a urethroscope at a very early age in these cases, but there will remain a few in which only a laparotomy can establish the diagnosis. Nevertheless, it should be clear from the present review that, unless the vaginal introitus is easily visible to external inspection, all equivocal cases are better reared as boys: not only are intersex males more common, but in the genetic females masculinization is due to the adrenal cortical secretions, the androgenic influence of which is such as to render them happier in the male role. Only in exceptionally rare cases, therefore, should it be impossible to give a confident opinion during the first weeks of life, and with the advance of paediatric surgery the age at which laparotomy may be safely undertaken is being rapidly reduced.

I should like to express my gratitude to Mr. Twistington Higgins and Mr. Denis Browne for their help and encouragement and for permission to publish details of cases under their care. My thanks are also due to Mr. Derek Martin, of the Hospital for Sick Children, for his excellent clinical photographs, and to Mr. Frank Price for his drawings. This work was undertaken during the tenure of the Leverhulme Research Scholarship of the Royal College of Surgeons, and I must acknowledge the kindness of the College authorities in allowing me to reproduce drawings of specimens preserved in the museum.

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AGRANULOCYTOSIS CAUSED BY AMIDOPYRINE

AN AVOIDABLE CAUSE OF DEATH*

BY

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Some years ago within a month I saw three necropsies on patients who had died of agranulocytosis. They were all males, patients of one surgeon, and, as they had all received full doses of sulphapyridine, the agranulocytosis was ascribed to this drug. Because there had been no similar cases in the rest of the hospital, I studied the matter further, and found that all three had received full but not excessive doses of either "cibalgin" or "veramon" during the weeks preceding death. I did not know these preparations, but Martindale's *Extra Pharmacopoeia* informed me that they were amidopyrine-barbiturate mixtures. It seemed more reasonable to assume that the amidopyrine had caused the agranulocytosis.

I was surprised to find that neither the surgeon, his registrar, nor his house-officer had realized that cibalgin and veramon contained amidopyrine. I was therefore not particularly surprised when other clinical pathologists told me of similar tragedies, or when I found it re-enacted in my own hospital.

Case Report

A woman aged 67 had had osteoarthritis of several joints, a duodenal ulcer, and early cardiac decompensation. In 1948 she was operated on for a strangulated hernia. On August 22, 1950, she developed a sore throat, which got worse until August 26, when she was referred to hospital and treated as an out-patient with penicillin and tab. codein. co.; she improved and was discharged on August 29. On September 6 she was again sent to hospital, very ill, prostrated, pale, dyspnoeic at rest, febrile, with a temperature of 101.4° F. (38.6° C.), a pulse of 125, and a very dry tongue. A diagnosis of bleeding from her duodenal ulcer was made, and she was admitted. (Hb, 8.9 g./100 ml.; blood urea, 76 mg./100 ml.; serum chloride, 84 mEq./litre; thymol turbidity, 5.5 units; flocculation positive.) Transfusion of 1,500 ml. of blood had little effect. On September 7 the white blood cells numbered 3,500 per c.mm., all lymphocytes. Treatment was ineffective, and she died that evening. Necropsy showed one ulcer and several superficial erosions in the pharynx, and a large pyloric ulcer, without

*Based on a paper read before the Association of Clinical Pathologists in January, 1951.

any evidence of recent bleeding. Sections of the bone marrow showed that all granulocytes had disappeared, and only plasma cells and a few erythroblasts could be seen.

The diagnosis of agranulocytosis having been established, her relatives were questioned, and they reported that she had taken "allonal" tablets. The patient's practitioner confirmed that she had prescribed at least six allonal tablets and probably more over a period. The practitioner did not know that allonal contained amidopyrine.

The patient presented a difficult diagnostic problem. The prostration, dehydration, and raised blood urea suggested bleeding from the peptic ulcer which was known to be present, but the fever and sore throat are not typical of bleeding. Pharyngeal ulceration was not present at the time of admission. The diagnosis of agranulocytosis was, in fact, made only after a blood count had demonstrated it, too late to benefit the patient. Now that antibiotics are widely used it seems probable that such atypical cases may become more frequent.

Preparations Containing Amidopyrine

Between 1934 and 1937 much publicity was given to the occurrence of agranulocytosis in subjects taking a patent medicine containing amidopyrine. Most practitioners believe that because of this publicity amidopyrine was removed from the proprietary medicines which had previously contained it. In fact, the only restriction imposed was to include amidopyrine in Schedule IV of the Pharmacy and Poisons Act, 1933, thus making it illegal to sell or distribute it or its mixtures except on the prescription of a registered practitioner. The patent medicines advertised direct to the public were either withdrawn or their composition was altered; but the ethical preparations which contained amidopyrine and were distributed under a proprietary name remained available to any practitioner, and can still be prescribed under their proprietary names. Some years ago Dr. E. N. Davey found 29 such mixtures available as tablets; most of these have disappeared, but there are still 10 makes of tablets which contain amidopyrine and are distributed under a proprietary name. These are: allonal* (Roche Products), amidophen (Eli Lilly), amyltal compound (Eli Lilly), cibalgine (Ciba), corosedine (Bengue), optalidon (Sandoz), somnosal (Napp), taumasthman (Wallace), veramon (British Schering), and veropyron (Gedeon Richter).

There is also a preparation intended for parenteral use—irgapyrin (Geigy); this is unlikely to be dangerous, because the injections will be given by the practitioner, and the presence of amidopyrine is clearly stated on the containers and leaflets.

Amidopyrine causes agranulocytosis in Great Britain to-day only when it is ordered as a mixture under a proprietary name by a practitioner who does not realize he is prescribing amidopyrine. The danger is simply that the practitioner rarely dispenses these mixtures himself, and easily forgets their composition once he has tried them and found them potent.

Incidence of Agranulocytosis

Most estimates of the incidence of agranulocytosis are guesswork. Recently 19 series totalling 3,344 patients who received parenteral amidopyrine were collected for me in Switzerland; of these, only four developed agranulocytosis, but many had received the drug for only a few days. Avery Jones (1947), in his Goulstonian Lectures, pointed out how such collected series or mass hospital statistics may be highly fallacious.

I have found three published experiments, and have private information of a fourth, in which amidopyrine was

*Since this paper was written Roche Products have announced that as from May 1, 1952, the amidopyrine in allonal would be replaced by isopropyl phenazone (*Pharmaceutical Journal*, May 3, p. 312). From now on, therefore, allonal is unlikely to be a cause of agranulocytosis, for isopropyl phenazone does not, so far as is known, cause agranulocytosis.

administered to a series of 200 or more patients for considerable periods—nearly all over 14 days, some over a year—under conditions such that agranulocytosis would have been recognized had it occurred (see Table).

Author	Route	Patients at Risk	Agranulocytosis		Deaths
			Cases	%	
Holten (1934)	Oral	352	5	1.42	5
Rawls (1936)	Oral	400	4	1.00	3
Gsell and Mueller (1950)	Parenteral	220	2	0.91	0
Cermák (1951)	Oral	300	0	0	0
Total		1,272	11	0.86	8

An incidence of 0.86% is so high that it seems barely credible, but, so far as I can judge, this is the best estimate yet available. It is possible that Cermák's experience represents a real difference in incidence, but one must remember that, were the true incidence of agranulocytosis 1%, there is 1 chance in 20 that no cases would occur in a series of 300 patients at risk.

Nevertheless, many practitioners knowingly use amidopyrine regularly, claiming that it and its mixtures with barbiturates are more potent than any other analgesic except opiates. They point out that amidopyrine is sold without restriction in France, Belgium, Germany, and Switzerland, deducing that it cannot be so very dangerous, and suggest that the fears expressed in Denmark, Great Britain, and the United States are exaggerated.

Those interested in the marketing of amidopyrine make other suggestions: that agranulocytosis is caused by impurities in some batches of amidopyrine (a possibility of little significance to the practising physician); or that the barbiturate of the mixture is the cause of agranulocytosis, ignoring the clear incrimination of the amidopyrine component by Madison and Squier (1934), Plum (1934, 1937), Israëls and Wilkinson (1937), and others, who produced severe leucopenia with fever and prostration by giving 0.2–0.5 g. of amidopyrine to patients convalescent or recovered from amidopyrine agranulocytosis.

It has also been suggested that agranulocytosis occurs only in patients whose bone marrow has been damaged by chronic infection. This may be true, but it does not help the practising physician. Infection is a common cause of pain, and an analgesic which damaged the marrow of infected patients only would be just as unacceptable as one which damaged normal marrow. A last suggestion is that the Anglo-Saxons form a racial group particularly susceptible to agranulocytosis. If we ignore the difficulty of defining an Anglo-Saxon, this hypothesis is quite attractive, and it is not difficult to assemble evidence to support it.

Personal communications from Professors Brüll, Govaerts, and Roskam, in Belgium, reveal that they have seen no cases of agranulocytosis attributable to amidopyrine during the past year or two, although amidopyrine mixtures are commonly used.

Dr. L. Cermák, of Prague, writes: "Amidopyrine is a drug very commonly used in Czechoslovakia, and up to the last few months it could be obtained without a prescription . . . so far as I could ascertain from the archives of the clinic, the occurrence of agranulocytosis as a clinical entity is negligible. In five years only four cases have been treated . . . I have studied the case histories of about 2,000 patients . . . from this point of view. The average amount of amidopyrine administered to one patient with chronic polyarthritis in the course of one year was over 1,000 g. Among all 300 patients I did not find one case of agranulocytosis."

Such clear-cut statements are difficult to explain away. It is unlikely that typical cases are missed, and sampling errors are not likely to be of significance. Taken together with the statement of one manufacturer, whose preparation is very popular in France and Switzerland, that no case of agranulocytosis following its use had ever been reported

to him, it seems very reasonable to consider whether there may be a significant geographical or racial variation in susceptibility to amidopyrine.

Nevertheless, Dr. Konrad Müller, of Westphalia, a physician, has seen four cases during the past four or five years—that is, as many cases as I have seen in 10 or 11 years, even though I have been a clinical pathologist serving 5 to 10 consultant physicians and a number of general practitioners. Rohr (1939) observed 16 cases in his clinic at Zurich between 1918 and 1939, and concludes that amidopyrine should be available only on prescription.

In 1931 Kracke observed that agranulocytosis was commoner in doctors, their wives, and in nurses than in other groups of the community, and attributed it to their greater use of benzamine compounds, derived from aniline; and in 1934 Kracke and Parker noted the low incidence in Great Britain, and hinted that the incidence was low because benzamine compounds were little used. The statistics available are incomplete and peculiar. They become somewhat less obscure when they are converted into cases per million inhabitants of the area considered; an incidence of one per million would be equivalent to about 45 cases in Great Britain.

Kracke and Parker's figures give, as total cases reported from all causes per million inhabitants: Germany 5, U.S.A. 3.5, France 2.5, Great Britain 0.12. Plum (1937), covering cases due to amidopyrine reported during the four years 1933–6, gives an annual incidence per million of U.S.A. 0.25, Germany 0.03, Great Britain 0.07, Switzerland 0.3, Sweden 0.46, and Denmark 2.9; if unpublished cases are added the Danish incidence swells to 4.8. If one assumes that Rohr's cases were all drawn from the canton of Zurich, the annual incidence is 1.3 per million. These figures appear fantastic. Denmark, Sweden, and Switzerland had at that time no restriction on the use of amidopyrine. Can the Danes be six times more susceptible than the Swedes, or can they have used six times as much amidopyrine?

A reasonable explanation can be offered by the observations of Plum (1937) and Dameshek and Colmes (1936). Plum suggests that one case is reported for every 65–70 kg. of amidopyrine imported into Denmark, while Dameshek and Colmes estimate one case for every 10,000 prescriptions; these estimates agree quite satisfactorily. Plum quotes cases in which the patient's medicine chest contained several packages of different proprietary medicines containing amidopyrine, and concludes: "It is extraordinarily difficult to obtain reliable anamnestic data . . . in several cases it has been necessary to investigate the stock of drugs on hand in the patient's home with the painstaking exactness of a detective, even though the relatives insisted that it would be useless to look." The Danish figures are high simply because Plum did work with the painstaking accuracy of a detective; and Rohr has high figures for Zurich because he is a haematologist of international repute to whom many of the recognized cases are referred. It seems probable that the incidence of agranulocytosis in a community which can buy amidopyrine freely must be of the order of two to five cases annually per million population, equivalent to 90 to 225 cases in Great Britain—at least, this appears to be reasonable for countries north and west of Czechoslovakia.

There is one observation which suggests that this estimate is too low. Stenbeck (1935, cited by Plum) introduced amidopyrine into his practice, and in the next six years observed 10 cases of agranulocytosis, which had previously been unknown. Even if we assume an improbably large practice of 10,000 souls, this is an incidence of about 150 cases annually per million inhabitants.

The Mechanism of Agranulocytosis

The direct toxicity of amidopyrine is negligible. Dameshek and Colmes stated that patients who have recovered from agranulocytosis caused by amidopyrine show no skin sensitivity to the drug, but show skin sensi-

tivity to a solution of amidopyrine in serum which has been allowed to stand for several days. In those skin-sensitive patients in whom it was tried, ingestion of amidopyrine caused leucopenia. Agranulocytosis therefore seems to be an allergic manifestation, requiring initial sensitization, followed after weeks, months, or even years by re-exposure to the drug. Since individuals vary greatly in their capacity to become sensitized to synthetic chemicals, there is bound to be great variation in the duration of the exposure to the drug before sensitization actually occurs.

Sensitization, and therefore agranulocytosis, will occur so long as amidopyrine is used. Most practitioners refuse to prescribe amidopyrine under its own name because they realize its danger—as a result, Bayer's original brand, "pyramidon," has been taken off the British market because the demand for it is negligible. Sensitization and agranulocytosis are being caused to-day by one or other of the 10 preparations listed above; and these preparations are often (but not always) prescribed in ignorance of the fact that they contain amidopyrine.

Substitutes for Amidopyrine

The excellence of amidopyrine-barbiturate mixtures as pain killers seems to depend on the combination of a peripheral vasodilator with a central sedative. There is no obvious reason why the dangerous amidopyrine should not be replaced by a less dangerous drug with similar pharmacological properties, such as acetylsalicylic acid, phenacetin, salicylamide, or mixtures thereof; and at least one firm has already issued such a mixture and requested its representatives to advocate its use in preference to their amidopyrine-barbiturate mixtures. It would undoubtedly be claimed that such mixtures were less effective than those containing amidopyrine, but now that Asher (1948) has shown how to compare the efficiency of analgesics it should be possible to settle this question by arranging a large-scale trial of the two types of mixture. Since any such trial would expose several hundred patients to the risk of agranulocytosis, it may be that it would be considered unjustifiable, but it might well save future generations all over the world from the risk of agranulocytosis, and I think such trials should be conducted.

Discussion

Such is the situation of amidopyrine. Its dangerous effects were well known 15 years ago, when Sir William Willcox found that as a component of a patent medicine it had killed a number of people. Is it possible to reduce its toll still further?

Before rushing to advise remedies for this specific case, it is well to consider whether it is unique; for, if it is not, remedies for other dangers should be considered at the same time.

Amidopyrine is not unique. A hypnotic, "sedormid," causes purpura, sometimes fatal, in patients who have been sensitized to it; Ackroyd (1949a, 1949b, 1949c) has demonstrated the mechanism of the purpura—a direct thrombocytolysis by the drug. Cryogénine (phenylsemicarbazide) is an antipyretic popular in France, and spasmodic attempts to introduce it into this country have been made. It causes haemolytic anaemia, and in March, 1950, Dr. Debré complained to the Academy of Medicine that during the previous year at the Enfants-malades he had seen six cases of haemolytic anaemia in children caused by it (Debré *et al.*, 1950). The cryogénine had been administered in suppositories advertised direct to the public under the name *Défébryl-enfants*. Buisine and Vincent (1950) reported a similar case in a child suffering from rubella complicated by agranulocytosis caused by the concurrent administration of "erythra"—a preparation of amidopyrine. Cryogénine is not on any poisons list in this country.

Clinical and forensic pathologists see too many tragedies due to drug idiosyncrasy. The Poisons Board is charged with the duty of making regulations to control the use of

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