It is clear that research is still needed to determine whether psychological or physio-pathological factors are the basis of addictive drinking. Although recent studies have indicated that the addictive phase of alcoholism may have a physical basis of a constitutional nature, psychotherapy is indispensable in its treatment, since the excessive symptomatic drinking (which is a pre-requisite for addictive drinking) is psychogenic or sociogenic, or both. Psychotherapy will, in most cases, need to be supplemented by the type of aid which a social worker can supply.

Certain drugs may prove to be a valuable adjunct to psychological and social therapy. Chief among these is tetraethylthiuramdisulphide, which causes a severe somatic reaction if the patient drinks alcoholic beverages when he is on a maintenance dose of the drug. This preparation should be available only to the medical profession and should preferably be employed only on cases in which continued supervision is possible. In more advanced cases of addictive drinking, other techniques such as the various forms of 'aversion' therapy—based on the use of apomorphine or emetine—may be more valuable. Even hormones such as ACTH or Cortisone have been reported to be effective in treating delirium tremens, acute alcoholic intoxication, and Korsakoff psychosis.

**AGRANULOCYTOSIS DUE TO ANTIHISTAMINE DRUGS**

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Agranulocytosis due to antihistamine drugs is rare, only seven cases having been recorded (Blanton and Owens, 1947; Clement and Godlewski, 1945; Cahan et al., 1949; Drake, 1950; Hilker, 1950; Martland and Guck, 1950) despite the extensive use of these drugs in recent years. It is thus thought worth while recording a case of agranulocytosis due to one of this group of drugs.

**CASE REPORT**

A 66-year-old Jewish widow was first seen on 24 February 1950 for severe coryza. Her previous history revealed that in August 1949 a cholecystectomy was performed for gall stones, with an uneventful recovery. Three weeks before the operation she had an attack of acute bronchitis, and was treated for five days with a compound sulphonamide, Sulphatriad, containing Sulphadiazine 0.185 gm., Sulphamerazine 0.13 gm., and sulphathiazole 0.185 gm. per tablet. One week before operation the blood urea was 23 mg. per 100 c.c., the prothrombin index was 95% and the haemoglobin 14.1 gm. per 100 c.c. of blood.

Her present complaints were severe nasal discharge and an irritating non-productive cough. There were no abnormal physical signs, apart from pyrexia of 99.4° F. Therapy consisted of a 'cough' syrup containing equal parts of 'Anodyne Pine Expectorant' Parke Davis (a mixture of various bark and root extracts with 3/16 grain of morphine acetate to the ounce) and 'Syrup Cocillana Co. B.P.C. 1949' to be taken in 1 drachm doses every four hours, and two tablets of Empirin Compound (Aspirin 3½ gr., Phenacetin 2½ gr. and Caffeine ½ gr. per tablet) twice daily, as well as 25 mg. of Phenendamine (Thephorin) thrice daily for four days. The condition abated rapidly, and within three days, she was well except for a slight cough. When seen again on 10 March, she stated that for a few days she had experienced weakness, a feeling of fullness above the eyes, cough productive of yellowish sputum, a tearing pain under the sternum on coughing, and pain deep to the xiphisternum on swallowing foods. She also complained that food did not go down easily, and that she had a continual feeling of pressure under the lower third of the sternum.

The temperature was 100.4° F., the pulse rate 120 per minute, and the blood pressure 130/80 mm. Hg. There were a few scattered medium crepitations at both lung bases. The area of stomach resonance appeared to be higher than usual. The diagnosis made was that of an acute upper respiratory infection involving the sinuses, trachea and bronchi. A liquid mixture of sulphonamide containing Sulphadiazine 5 gm. and Sulphathiazole 5 gm. to the 100 c.c., in a base containing sodium citrate
Until 20 March the temperature varied between 99°F and 103°F. On 20 March slight ulceration round her only tooth—a right lower molar—was seen, but no other ulceration was present. Cough and painful dysphagia were troublesome until 27 March, when improvement started and permitted a reduction in the frequency of the pentnucleotide and antibiotic injections to 8-hourly injections. A pyrexia of 103°F to 104°F continued until 26 March, when it started to come down gradually, and by 29 March it returned to normal. On 23 March she developed sordes on the lips, and on 27 March a solitary pin-point ulcer appeared at the junction of the hard and soft palates. At times she was delirious. Profuse night sweats commenced on 26 March and recurred nightly until the temperature settled on 29 March. By 30 March, the sordes had disappeared, the palatal ulcer was healed and the patient was ambulatory. On 31 March the pentnucleotide was reduced to 10 c.c. twice daily because of sweating and vomiting following the injections, but the antibiotics were continued 8-hourly until 3 April. On 4 April, pentnucleotide was reduced to 10 c.c. daily and was finally discontinued on 9 April. By 5 April, ulceration round the tooth had disappeared, and the patient felt much stronger.

Further clinical progress was uneventful until her discharge on 22 April, when she weighed 131 lb., compared to 135 lb. on admission. The Penicillin and Streptomycin were reduced to 12-hourly injections on 3 April, and were reduced in dose to 250,000 units penicillin and 0.25 gm. Streptomycin twice daily on 10 April. On 12 April, 2 c.c. crude liver extract and 1 c.c. vitamin B compound were given daily by injection, as well as 2 capsules of Campobiol (vitamin B Compound and 100 mg. ferrous sulphate per capsule) orally thrice daily. On 14 April, the Streptomycin and crystalline Penicillin were stopped, and replaced by one daily injection of 600,000 units of aqueous Procaine Penicillin G. On 19 April all injections were stopped, but she took oral Campobiol and folic acid until her discharge on 22 April.

The clinical improvement was paralleled by the haematological picture, and from 27 March, there was a progressive increase in the percentage and absolute numbers of neutrophils, although the total leucocyte count remained below 1,500 per c.mm. for a further week. (Table 1 and Fig. 3.) From then onwards, the total leucocyte count and absolute number of neutrophils continued to increase. On 3 May the leucocyte count was 3,300 per c.mm., but the sternal bone marrow reflected a dramatic return to normal haematopoiesis, although the marrow was still hypoplastic. The myelogram showed a total nucleated count of 18,000 with blast cells 1%, premyelocytes 2%, myelocytes 3%, metamyelocytes 6%, stab cells 3%, polymorphonuclears 0%, lymphocytes 26%, monocytes 5%, erythroblasts 1%, proerythroblasts 4%, early normoblasts 5%, intermediate normoblasts 20%, late normoblasts 20%. This was interpreted as showing 'a severe depression of the granular series with defective maturation.' There was no disturbance of the erythropoietic mechanism, with a relative increase in that series. (Table 1 and Fig. 3.) From then onwards, the total leucocyte count and absolute number of neutrophils continued to increase. On 3 May the leucocyte count was 3,300 per c.mm., but the sternal bone marrow reflected a dramatic return to normal haematopoiesis, although the marrow was still hypoplastic. The myelogram showed a total nucleated count of 18,000 with blast cells 1%, premyelocytes 2%, myelocytes 3%, metamyelocytes 6%, metamyelocyte eosinophils 2%, stab cells 10%, polymorphonuclears 32%, polymorphonuclear eosinophils 4%, lymphocytes 18%, monocytes 2%, erythroblasts 1%, proerythroblasts 1%, normoblasts—early 4%, intermediate 6%, late 7%—plasma cells 1%.

On 4 June she developed an upper respiratory infection with a temperature of 100.4°F. Her leucocyte count at this time was 6,700 per c.mm. with 76% neutrophils, indicating a return to normality. The following day her temperature was normal, and she has remained well.
DISCUSSION

Although it is impossible to say with certainty that the antihistaminic was responsible for the agranulocytosis, it appears to be the likely cause. It cannot be denied that the course of sulphonamides in August 1949 may have sensitised her, and that the sulphonamide mixture given in March 1950 may have been the etiological factor, but against this is the fact that the symptoms, including dysphagia, were already present when the sulphonamides were started. The phenacetin in the Empiria compound can be dismissed as a cause because, after her recovery from the agranulocytosis, she had repeated doses of this drug for the upper respiratory infection in June 1950, with no adverse effect on the neutrophil response. The only proof would be a therapeutic trial with the Phenendamine, but in view of the serious nature of the disease this procedure must be deemed unjustifiable.

Seven cases of agranulocytosis due to antihistaminic drugs have been reported in the literature. In the reported cases the period of administration has been from three to eight weeks, and the present case would appear to be unusual in that only 300 mg. of Phenendamine were taken over five days. Blanton and Owens (1947) reported the case of a widow aged 73, who was given 10.75 gm. of Methaphenilene (Diatrin) over a period of five days. His white cell count went down to 1,000 with complete disappearance of the neutrophils. He had made a good recovery on treatment with Penicillin and Dihydrostreptomycin. Clement and Godlewski (1945) reported the first case of agranulocytosis due to an antihistamine drug in a girl of 13½ years, with asthma, after she had received three weeks of treatment with a synthetic antihistamine 2339 RP (N-Benzyl-N-phenyl-N, N-dimethyl-ethylenediamine-chydrochloride). Two further cases have been reported both due to Pyribenzamine (Hilker, 1950; Martland and Guck, 1950). In one case 50 mg. was taken three times daily for eight weeks by a 39-year-old nurse, and in the other, eighty-five 50 mg. tablets were taken over a five-week period by a female aged 60 years. Neither case was fatal. Thus, of the reported cases, the drug used was Pyribenzamine in five, Methaphenilene (Diatrin) in one, and antihistamine agent 2339 RP in the remaining case. The present case would appear to be the first due to Phenendamine. Fortunately all eight cases have recovered.

In the production of agranulocytosis Kracke (1934) has stressed the importance of the benzene ring in combination with nitrogen or the amino (NH₂) group, making substituted primary amines. Many of the antihistaminic agents, such as Pyribenzamine and Methaphenilene, contain this so-called 'benzamine linkage' (Fig. 1), as do some of the sulphonamides, but others such as Diphenhydramine (Benadryl) have no such linkage, and have never been known to cause agranulocytosis. Other antihistaminics such as Mepyramine maleate (Anthisan) contain a 'benzamine linkage' in their structure, but despite extensive use, have not as yet been reported to cause agranulocytosis. Both Tripellenamine (Pyribenzamine) and Methaphenilene (Diatrin) are ethylenediamines, but Tripellenamine contains a pyridine ring structure, as do Anthisan, Histadyl and Thelenylene. Methaphenilene (Diatrin) differs from the above group by substitution of a phenyl ring for the pyridine structure (Loew, 1950). Phenendamine (Thephorin) is not closely chemically related to any of the other antihistamine agents (Loew, 1950), and study of this structure indicates that it does not contain a benzamine linkage (Fig. 2). It has the chemical designation of 2-methyl-9 phenyl-tetra-hydro-pyridinene hydrogen tartrate. This structure contains two intramuscular Penicillin. These writers also mention another case of a patient who took approximately 400 mg. of Pyribenzamine for a month before the onset of agranulocytosis. The white cell count declined to 1,100 and the neutrophils disappeared completely. She made an uneventful recovery. Drake (1950) reported a case of agranulocytosis in a man aged 81 who suffered from an allergic condition of the nasal mucosa, and took approximately 7.4 gm. of Methaphenilene (Diatrin) over a period of 6½ weeks. His white cell count went down to 1,000 with complete disappearance of the neutrophils. He made a good recovery on treatment with Penicillin and Dihydrostreptomycin.
benzene rings, as does the agent 2339 RP used by Clement and Godlewski (1945) and Drake (1950) points out the possibility that such a chemical structure increases the probability of granulocytopenic effect. It is thus obvious, owing to the widely different chemical characteristics of the antihistamine group of agents, and the fact that some with a 'benzamine linkage' have produced agranulocytosis while others have not as yet done so, that only future experience will tell which are capable of causing granulocytopenic effects.

There are other interesting features in the present case. Damashek (1944) stated that 'a patient (with agranulocytosis) over 60 years of age has hardly any chance'. Furthermore, the lower the total leucocyte count the worse the outlook, recovery being exceptional with counts under 1,000 per c.mm. He considered a complete lack of granulocytes to be of no great prognostic significance. In the present case, despite the patient's being over 60 years and the count going as low as 500 on two occasions, she made a good recovery. This must be attributed to modern antibiotic treatment. The type of marrow found in this case with the presence of granulocyte precursors indicates a better outlook, than in those cases in which only lymphocytes are found (Damashek, 1944).

A further feature of interest in this case is the paucity of ulcerations in the mouth, and the presence of painful dysphagia as the main symptom.

**SUMMARY**

1. A case of agranulocytosis has been recorded.
2. The possibility that the condition was due to an antihistamine drug has been discussed.
3. Seven other cases reported in the literature are reviewed, making a total of eight cases to date in which antihistamine drugs could be incriminated as the cause of agranulocytosis.

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**REFERENCES**


