STEVENS-JOHNSON SYNDROME AND GRANULOCYTOPENIA AFTER PHENYLBUTAZONE

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The toxic effects of phenylbutazone ("butazolidin") were reviewed in a leading article in the *British Medical Journal* (1952), and include skin rashes, water retention, activation of peptic ulceration, agranulocytosis, and a tendency to haemorrhage, which is sometimes associated with thrombocytopenia.

The following case developed Stevens-Johnson syndrome and granulocytopenia.

Case Report

A housewife aged 50 had pain and stiffness in the neck, shoulders, and left elbow for two years following the menopause. There was a history of eczema in childhood and psoriasis of the elbows, but no evidence of allergy in her family. She bought some phenylbutazone, which was obtainable at that time without a doctor's prescription, and took 200 mg. twice daily for 13 days until her symptoms were relieved. No other drugs were taken. Four days later (April 20) her mouth and tongue began to swell and her throat became painful on swallowing. The next day a non-irritating macular erythema appeared on the face, trunk, and limbs, accompanied by pyrexia and headache. On April 22 the conjunctivae were involved and the mouth became ulcerated. On April 23 she was admitted to hospital severely ill, with a pyrexia of 103.4° F. (39.7° C.). The skin eruption consisted of a generalized erythema exudativum multiforme. Discrete bullae appeared on the trunk, while large confluent blisters, containing serous fluid, formed on the distal portions of the limbs. The nail folds of the fingers and toes were swollen and inflamed. A foul stomatitis, with ulceration of the buccal mucous membrane, fauces, and tongue, was accompanied by haemorrhagic crusting of the lips. Purulent conjunctivitis and blepharitis were present. A few cervical glands were enlarged, but there was no generalized lymphadenopathy, and the spleen was not palpable.

Investigations.—No predominant organisms were grown from the throat and conjunctivae, and the fluid from the blisters was sterile. The urine contained a moderate amount of albumin, but no cells, and was sterile on culture. The blood urea was 16 mg. per 100 ml. A blood count showed a normocytic normochromic anaemia and granulocytopenia, with R.B.C. 3,990,000 per c.mm.; Hb, 11.5 g. per 100 ml.; W.B.C., 2,800 per c.mm. (juveniles 3.5%, band forms 21.5%, segmented forms 17%, eosinophils 4%, basophils 1%, lymphocytes 43.5%, monocytes 9.5%). The platelet count was 233,000 per c.mm. The bleeding-time was 3½ minutes, and Hess's test was faintly positive.

The sternal marrow on admission showed a low cellularity and numerous myeloid precursors. Depressed marrow activity was combined with maturation arrest. The marrow count was 30,000 nucleated cells per c.mm. (neutrophil polymorphs 5%, neutrophil metamyelocytes 35.5%, neutrophil myelocytes 23.5%, promyelocytes 4.5%, myeloblasts 0.5%). The myeloid/erythroid ratio was 4.8/1.

Treatment.—Aqueous penicillin, 500,000 units, was given six-hourly and diphenhydramine hydrochloride ("benadryl"), 50 mg., three times a day. The conjunctivitis, stomatitis, and skin lesions were treated with local bland applications. During the first week there was steady improvement, and

the pyrexia subsided. The conjunctivitis cleared up rapidly and the eruption began to subside.

The blood picture on the fourth day of treatment showed R.B.C., 3,560,000 per c.mm.; Hb, 9.5 g. per 100 ml.; W.B.C., 6,200 per c.mm. (juveniles 0.5%, band forms 7%, segmented forms 75%). The marrow count was 50,000 nucleated cells per c.mm. (neutrophil polymorphs 15%, neutrophil metamyelocytes 26%, neutrophil myelocytes 18.5%, promyelocytes 5%, myeloblasts 1%). The myeloid/erythroid ratio was 12.7/1.

During the second week desquamation began, leaving residual pigmentation. Shedding of the nails of the fingers and toes occurred. The stomatitis began to improve. The blood picture at the end of the second week had returned to normal with the exception of the anaemia. Blood count showed: R.B.C., 3,710,000 per c.mm.; Hb, 10.3 g. per 100 ml.; W.B.C., 6,200 per c.mm. (juveniles 0%, band forms 5%, segmented forms 76.5%). The marrow count was 80,000 nucleated cells per c.mm. (neutrophil polymorphs 27.5%, neutrophil metamyelocytes 29%, neutrophil myelocytes 7.5%, promyelocytes 3%). The myeloid/erythroid ratio was 2.8/1.

By the end of the fourth week healing of the lesions was complete and the patient was feeling well.

Discussion

The clinical picture at the height of the reaction was similar to cases of Stevens-Johnson syndrome reported by Thomas (1950), some of which followed the use of sulphonamides. In this case sensitivity to phenylbutazone seems to have been the cause.

The granulocytopenia which occurred was similar to the type recorded in several cases by Hinz *et al.* (1953) and Werblow and Neber (1953). The marrow was of low cellularity and the development of myeloid cells was arrested at the myelocyte/metamyelocyte stage. The presence of numerous mitoses among these cells indicated a good prognosis. There was no reduction of the platelet count.

The marrow count and the white-cell count of the peripheral blood had returned to normal by the end of two weeks, although a moderate degree of anaemia persisted. The speed of this recovery compared favourably with those cases treated with cortisone or adrenocorticotrophin (A.C.T.H.) which were reported by Hinz *et al.* and Werblow and Neber.

The *British Medical Journal* (1952, 1953) stressed the need for careful assessment of each case before prescribing phenylbutazone, and advised that the daily dose should not exceed 600 mg., as the frequency of toxic reactions reported seemed to vary in proportion to the dosage used. In this case both the daily dose (400 mg.) and the total amount taken (5.2 g.) were small, and there was also a delay of four days between the discontinuance of phenylbutazone therapy and the appearance of symptoms. The severity of the reaction provoked by this small dose suggests an allergic type of response. It seems, therefore, that the greatest caution is advisable in prescribing phenylbutazone when there is any past or family history of allergy.

Summary

A severe case of sensitivity to phenylbutazone is described. The features were those of Stevens-Johnson syndrome and granulocytopenia.

Penicillin and diphenhydramine hydrochloride but not cortisone or A.C.T.H. were used in treatment. The patient made an uneventful recovery.

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