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SULPHONAMIDE INTOLERANCE

By DAVID ERSKINE, M.D., D.P.H. (Medical Officer, Guy's Hospital and Canterbury V.D. Clinics, and Dermatologist to the Seamen's Dreadnought Hospital, Greenwich).

THE considerable incidence of intolerance to sulphonamide therapy causes many difficulties in treatment; it is important that the symptoms resulting from this intolerance should be well recognised and their significance appreciated, for it is not always necessary to discontinue the drug. In view of the reported toxicity, there is a tendency among practitioners to give small and often inadequate doses of the compounds with the result that clinical response is often delayed or absent while, frequently, a degree of intolerance still occurs. There is evidence that a resistance to the drug occurs when the dosage is at first small and in many of these cases therapeutic effect is not obtained by a later full dosage. Further, an essential of efficient medication is that the dosage should be evenly spaced so that the blood content can be maintained, as nearly as possible, constant; that is to say, 8 hourly and *not* "Three times a day" or 6 hourly and *not* "Four times a day." It is also well recognised that sulphonamide therapy should continue for an optimum period after apparent cure as otherwise morbid conditions are liable to recur.

The degree of intolerance appears to bear a relationship to the therapeutic efficiency of the particular compound employed; certain individuals also appear to be more susceptible to the drugs, possibly exhibiting an idiosyncrasy, and show a higher degree of intolerance. Many patients complain of malaise when commencing treatment with sulphonamides, but the symptoms usually diminish after forty-eight hours and most patients can then continue medication without difficulty.

The more common minor manifestations of intolerance are headache, indigestion, malaise and nausea. These symptoms occur early in treatment and are usually of short duration. They can frequently be relieved by the

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administration of sodium bicarbonate or a mild gastric sedative, but the more persistent cases, occasionally with severe gastritis, vomiting and enteritis, may cause considerable anxiety and require administration of the compounds by the injection of one of the soluble solutions. A frequent symptom reported by patients under treatment with sulphanilamide is a mild tingling of the hands and feet usually with no objective evidence of an organic lesion; this symptom may, however, be related to the occasional occurrence of peripheral neuritis which is now well recognised after the administration of a certain compound of the group.

Undesirable effects of the drugs on the bone marrow have been reported by several workers and appear to occur to a greater or lesser degree with all compounds of the group. Attention to the occurrence of a polymorphonuclear leucopænia in a proportion of cases was made by Britton and Howkins (1938) and Lloyd, Erskine and Johnson (1938); the latter writers were of opinion that with treatments of short duration this effect was not a serious contra-indication to chemotherapy, as a normal blood condition was apparently rapidly regained after discontinuation of treatment. Cases of agranulocytosis have been ascribed to sulphonamide compounds, usually after very high dosage (Nicol and Freedman, 1939), and Colebrook (1939) collected 35 cases in a complete review of the literature over two years; he stated that he knew of other cases which had not been reported and suggested that, as the angina syndrome occurred in only about one of 5 cases of agranulocytosis, it was probable that further cases had occurred but had not been diagnosed. He, too, observed that most cases had occurred after comparatively high doses and drew attention to the narrow margin of safety which appeared to exist between the necessary therapeutic dose and that which was liable to cause serious damage to the bone marrow. He stressed the importance of frequent blood examinations in cases undergoing prolonged chemotherapy and referred to the danger of continuing administration in cases which did not show an early response to the drug.

It is probable that certain unexplained cases of "Drug Fever" may in reality be cases of an abortive type of agranulocytosis and the occurrence of Drug Fever, in view of its symptom similarity to the onset of the more

serious condition, should in all cases be considered an indication for a complete blood examination.

The effect of the drug on the red marrow is less marked, but a diminution of the hæmoglobin percentage has been observed and cases of hæmolytic anæmia are reported (Jennings and Southwell-Sander, 1937). Cyanosis, with and without methæmoglobinæmia and sulphhæmoglobinæmia, is a manifestation of intolerance which has received considerable attention by several workers, but which would appear to occur less frequently during the administration of sulfapyridine. A urinary excess of urobilin, hepatitis and jaundice have occasionally been observed and McCann (1939) and others have drawn attention to the occurrence of hæmaturia.

Recently, the suggestion that encephalomyelitis occurring in two patients after treatment with sulphanilamide may be a toxic manifestation of the drug (Fisher and Gilmour, 1939) shows that our knowledge of the dangers attendant on the administration of these compounds is not yet complete. It should however be recognised that these manifestations of toxicity are comparatively rare and are not contra-indications to the administration of the drugs for conditions in which they are indicated; they do however indicate the importance of careful observation in all cases which are undergoing treatment so that these undesirable side effects can be minimised by early corrective treatment.

Apart from the gastric cases already mentioned, the most frequent manifestation of intolerance to these drugs is the appearance of a sulphonamide dermatitis. Considerable attention has recently been drawn to these skin rashes and their variation in type. It seems probable that cases of sensitisation and of drug retention occur, but the factors are so variable and the incidence so frequent that a brief description of illustrative cases will be of interest. These rashes may occur during the first course of treatment or only on subsequent courses; they may occur with every course of treatment, and with all or only one of the compounds of the group. The only constant factor is the tendency for the rash to occur between the eighth and fourteenth day of administration, so that whenever possible from a clinical consideration the restriction of therapy to seven days will almost entirely remove this complication which the patient finds so distressing.

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TYPICAL CASES

Case I.—MORBILLIFORM ERUPTION.—Male, aged 23, took 30 gm. of M. & B. 693 in ten days. At this stage

FIG. 1.—Case I. Morbilliform Type of Eruption due to M & B 693 ; photographed on the second day of rash.

he complained of generalised irritation of the skin, and one day later developed a profuse morbilliform eruption on the trunk, face, neck and thighs with a rather less

profuse rash on the arms and legs. The eruption was slightly bluish-red in colour and tended to be papular. There was mild pyrexia and malaise. The drug was discontinued and the rash faded in one day.

Case 2.—SCARLATINIFORM ERUPTION.—Female, aged 29. After 35 gm. of Sulphanilamide in eleven days, she was found to be covered with a non-irritating punctate erythema; the rash was intense on the forearms and outer aspects of the upper arms, but rather fainter on the chest and back, while the face was clear. This eruption had been preceded by one day of malaise and shivering.

Case 3.—URTICARIAL ERUPTION.—A female, aged 20, had felt "dopey" while taking 20 gm. of M. & B. 693 in ten days. She then developed irregular patches of irritating erythema. The drug was continued and further lesions tended to occur for a day or two, but after the fourth day no further patches were observed.

Case 4.—Male, aged 39. 42 gm. of Sulphanilamide in fourteen days. He developed an acute generalised urticaria and was treated (in the Casualty Department) with adrenalin. Seven days later, he was given further sulphonamide treatment and took $7\frac{1}{2}$ gm. of the same drug in five days without intolerance.

Case 5.—PAPULAR ERUPTION.—Male, aged 37, had taken 24 gm. of M. & B. 693 in eight days when a rash appeared at the bend of the elbow after a blood test. The rash was seen on the following day; it was a fine, discrete papular eruption on the arms and trunk, and it appeared to be causing severe irritation. The drug was discontinued and the rash completely disappeared in two days.

Case 6.—LIGHT SENSITISATION TYPE.—Male, aged 43, took 30 gm. of Sulphanilamide in ten days, and then developed an œdematous, urticarial erythema of the hands and face with many bullæ on grossly œdematous ears. The œdema and eruption were limited to the exposed areas. The drug was discontinued and the condition subsided in three days. Five weeks later, 1 gm. of M. & B. 693 three times a day was prescribed, and on the eighth day of this course he again developed an exactly similar eruption on the exposed areas which faded four days after discontinuing the drug. The urine was dark, and there was a weakly positive indirect Van den Berg reaction. One year later, chemotherapy was

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again administered and on the third day he noticed generalised irritation of the skin as on the previous occasions. The drug was immediately stopped and no further symptoms occurred.

FIG. 2.—Case 6. Light Sensitisation Eruption, photographed on second day. Showing œdema and limitation to the exposed areas.

Case 7.—SENSITISATION TO THE COMPOUNDS.—A male, aged 21 years, took 34 gm. of M. & B. 693 in fourteen days. On the tenth day he complained of a sore throat, and this was followed by a period of malaise; on the fourteenth day, his private doctor diagnosed scarlet fever and sent him to a Fever Hospital where the diagnosis was in doubt, partly on account of the rash being severely irritating. Three weeks later, he took one tablet of

M. & B. 693 and within a few hours developed a sore throat and generalised scarlatiniform rash which lasted only one day. Two months later a single tablet again reproduced the same evidence of immediate intolerance.

Case 8.—A male, aged 26, was treated with M. & B. 693, 1 gm. t.d.s. He took 24 gm. in ten days with no evidence of intolerance, but there was a delayed clinical response. After an interval of twelve days, he took two tablets (1 gm.) of M. & B. 693 and rapidly became "hot all over"; he took further tablets and was seen a few hours later with a generalised scarlatiniform erythema. T. 99.8°; P. 110; faucial inflammation and suffused conjunctivæ. Although the drug was continued, the rash faded in twenty-four hours. A further 24 gm. of the drug were administered and there was no further ill effect. This patient has also had two further courses of sulphonamide without any drug symptoms.

Case 9.—ŒDEMA OF THE LARYNX. A more serious indication of intolerance was observed in an elderly male patient with lupus erythematosus. He had been given Sulphanilamide, but this was discontinued after a few days on account of symptoms of intolerance. One year later it was decided to try the effect of M. & B. 693 which was then available. On account of the previous intolerance, an initial dose of one half gram tablet was given; eight hours later he developed dyspnoea, swelling of the tongue and face with cyanosis and oedema of the larynx. The condition was relieved by adrenalin and intravenous calcium gluconate; no further sulphonamide was, of course, administered. A reaction of this type, although probably extremely rare, serves to indicate the danger of haphazard treatment with these drugs and the need of special care in treating cases who are thought possibly to be sensitised to the compounds.

The appearance of a sulphonamide dermatitis is not of serious significance. If medication is stopped, the rash will probably disappear in a few days. In certain conditions, however, cessation of therapy will be undesirable from the clinical point of view and it is therefore interesting to note that many of the eruptions will rapidly clear even if the drug is continued in the same or diminished dosage (Erskine, 1939). This is particularly likely when there is no drug retention. It has been suggested (Tedder, 1939) that the various pictures of sulphonamide

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dermatitis cannot be explained by a single theory of causation and that drug retention, sensitisation, liberation of toxins (Barber, 1938 ; Erskine, 1938) and the appearance of photo-sensitising agents (Rimington and Hemmings, 1938) all play a part in different cases. The possibility of a light sensitisation type of eruption should be remembered and excessive exposure of the patient to real or artificial sunlight, especially during treatment with Sulphanilamide, should be avoided. When this type of eruption occurs, it is desirable that the drug should be discontinued. In certain other cases, when the urinary elimination has been found satisfactory (Werner, 1939) treatment has been continued with a possible desensitisation of the patient ; these cases frequently show no intolerance on later administration of the compounds, whereas when the drug has been stopped on account of the appearance of an eruption, subsequent eruptions often occur during later courses of treatment. This continuation of therapy should be attempted only when the patient is under continued observation so that any exacerbation can be immediately controlled.

SUMMARY

Although the manifestations of intolerance to the sulphonamide group of drugs are varied and undesirable, they are seldom of serious import ; when the extensive use of these drugs is considered, it will be realised that the incidence of grave intolerance is rare. It is, however, apparent that the closest observation of cases under treatment is desirable so that toxic effects can be controlled at the earliest indication. Cessation of therapy is not always indicated when intolerance occurs, indeed it is often not desirable ; a proper evaluation of the signs and symptoms will lead to an appreciation of the indications for or against further administration of the compounds.

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