of the heart, spontaneous beating recommenced, while blood pressure, pulse, skin colour, and pupils returned to normal. It was then discussed whether or not operation should continue, and it was decided to proceed with the skin grafts. For adequate working function of the patient's hands and a good result for the face they must be grafted as soon as possible, as in a subsequent anaesthesia he might develop an irreversible cardiac arrest. The operation lasted two hours (including cardiac arrest) without further incident, and the patient awoke immediately after extubation. He made an uneventful recovery except for a transient pleural effusion, which was tapped under local analgesia without further recurrence. Electrocardiograms taken on March 23, 27, 28, and 30 were normal.

The patient left hospital two weeks after the grafting. When seen three months later his hand function was fair, though he was still very anxious. Otherwise cerebral function was good. Later, operations were carried out seven times on the hands and face under local analgesia. On the hands the method used was brachial plexus block. There has been no further incident in connexion with these anaesthetics. When the patient was seen again one year and three months later, his anxiety was much less and the electrocardiogram continued to be normal.

Discussion

That cardiac arrest followed the fourth and sixth anaesthetics with intubation, but not the fifth without intubation, suggests that intubation triggered off cardiac arrest. Why this had not occurred after any of the first three intubations is not clear, but the patient's increasing fear may have passed a critical point at the fourth anaesthesia. The resulting increased reflex excitability, together with the viscerocardiac reflex (Keating, 1956) from intubation, might then have been enough to stimulate cardiac arrest. It seems clear that the possibility of cardiac arrest on intubation should be kept in mind if a patient comes to operation in great fear and/or pain. If it is possible to avoid intubation, other methods of anaesthesia should be employed. However, if (a) cardiac arrest has occurred, (b) the patient is young and otherwise healthy, and (c) cardiac resuscitation is successful with circulation restarted within the safety time-limit (less than three minutes without anoxia preceding the cardiac arrest) it is recommended that the operation be continued.

Summary

A case report is presented of a patient, in great pain and anxiety, who on two occasions developed cardiac arrest immediately after intubation.

On the first occasion, following successful cardiac resuscitation, the operation was postponed, but after the second successful resuscitation, operation being urgent and the patient young and otherwise fit, it was completed without further incident.

It is suggested that cardiac arrest under anaesthesia for an urgent operation, in a young and otherwise fit patient, need not warrant postponement of the operation if the heart can be successfully restarted.

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HEINZ-BODY ANAEMIA DUE TO DAPSONE

BY

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Dapsone (diaminodiphenyl sulphone), originally introduced for the treatment of leprosy, has since 1953 (Kruizinga and Hamminga, 1953) been used in the treatment of dermatitis herpetiformis. Many authors have found it of great value (Vickers, 1954; Morgan *et al.*, 1955; Alexander, 1955), and it is preferred by many doctors and their patients to sulphapyridine, liquor arsenicalis, etc., which had previously been used to suppress the symptoms of this condition.

In dermatitis herpetiformis the minimum dose of dapsone required to suppress the symptoms varies greatly in different patients, some requiring as much as 200 mg. daily, while others are controlled by 50 mg. daily or less. Side-effects during dapsone therapy are common. The manufacturers give warning of the dangers of haemolysis; other side-effects which have been reported are liver damage, drug rashes, depression, which can be very severe, and, recently, agranulocytosis (McKenna and Chalmers, 1958).

It is well recognized that anaemia, sometimes severe, can occur during the course of dapsone therapy (Allday and Barnes, 1951; Kruizinga and Hamminga, 1953; Morgan *et al.*, 1955; Alexander, 1955). Early recognition of the onset of this state is important, and the detection of Heinz bodies is a most useful test. These are small refractile granules found in the red blood cells in many cases of drug haemolytic anaemia. They cannot usually be seen in a routinely stained blood film, but they are readily demonstrated by a simple technique, using a supravital stain.

Numerous Heinz bodies were found in a patient (Case 1) who developed haemolytic anaemia while taking dapsone, and as a result of this finding we performed the test in other patients.

Technical Methods

Demonstration of Heinz Bodies.—Method I:—A few drops of blood are mixed with about double their volume of 0.5% methyl violet in isotonic saline (this solution must be filtered before use). After standing for a few minutes, a drop is examined under a coverslip with the oil-immersion objective. *Method II* (permanent preparations):—A few drops of blood are mixed with about twice their volume of isotonic saline. The tube is centrifuged until the cells are deposited and the supernatant fluid is poured off. The cells are resuspended in a solution of 0.5% methyl violet in isotonic saline (filtered immediately before use). The tube is centrifuged again and films are made at once from the deposit; these are air dried and mounted without any fixation or counterstain.

Blood may be taken by finger prick or by venepuncture into citrate or ethylenediamine tetraacetate (E.D.T.A.). By either of the above methods Heinz bodies are shown as darkly stained discrete

particles. The red cells are pale yellow, almost colourless; reticulocytes show a diffuse mauve mottling.

Other Methods.—All other haematological techniques used were those recommended by Dacie (1956).

Case 1

A 76-year-old farmer had been well until August, 1956, when he first noticed a blister on his left thigh. He attributed this to a hot-water bottle burn, although he could not remember having burned himself. Healing was very slow. From that time onwards he developed many more small blisters; they appeared on normal-looking skin, were extremely itchy, and on bursting left indolent ulcers. He was admitted to hospital on March 27, 1957, when he was found to have widespread dermatitis herpetiformis. He was hypertensive (blood pressure 210/110 mm. Hg). In spite of local treatment combined with bed rest, his condition became worse.

Twelve days after admission he was given dapsone 50 mg. daily; after three days this was increased to 100 mg. twice daily. Three days later, on April 14, no new blisters were developing, and the dapsone seemed to control his dermatitis herpetiformis adequately. However, on April 26 he went into cardiac failure but responded well to treatment with digoxin, aminophylline, and mersalyl. Dapsone was continued, and subsequently he developed a haemolytic anaemia. By June 4 he was cyanosed; his haemoglobin

FIG. 1.—Course and treatment in Case 1.

FIG. 2.—Heinz bodies in the blood in Case 1.

had fallen to 72% (10.7 g./100 ml.), and Heinz bodies were found in 50% of his red blood cells. A blood film showed numerous fragmented red cells, and the reticulocyte level was 10%. The white-cell count was 17,800/c.mm.; a small quantity of methaemoglobin was detected in the red cells; the red-cell osmotic fragility was normal. Dapsone was at first reduced in dosage, then withdrawn. The Heinz bodies gradually disappeared and fragmented cells were no longer seen in the blood films. Fig. 1 summarizes the findings in the blood during this period; Fig. 2 is a photograph of the blood on June 4, stained to demonstrate the Heinz bodies.

Case 2

A married woman aged 52 first developed dermatitis herpetiformis in 1932. She had not noticed any relief from her itching until 1955, when she began treatment with sulphapyridine (0.5 g. twice daily). By 1957 the dermatitis herpetiformis was well controlled. Her blood picture at this time was normal; on May 13 her haemoglobin was 92% (13.6 g./100 ml.) and white cells 7,800/c.mm. As she felt very depressed, on June 24 the sulphapyridine was replaced by dapsone 100 mg. twice daily. On July 22 a blood count showed a haemoglobin level of 72% (10.7 g./100 ml.), the white-cell count was 9,300/c.mm., and some fragmented cells were seen in a blood film.

Unfortunately the test for Heinz bodies was not carried out on July 22; the patient was seen again 48 hours later for this purpose, when Heinz bodies were found in 40% of her red blood cells, and a reticulocyte count was 8%. Dapsone was discontinued and sulphapyridine (0.5 g. twice daily) restarted. Her dermatitis herpetiformis has been well controlled on this dose.

Case 3

A married man aged 56 was quite well until 1953, when he developed dermatitis herpetiformis. He began treatment with sulphapyridine 0.5 g. twice daily in 1954, but had to stop this after three months because of malaise and headaches. In 1955 treatment with dapsone was instituted, beginning with a dose of 100 mg. daily and later increased to 100 mg. twice daily. His itching became well controlled after two months, and he was gradually able to reduce the dose to about 100 mg. every third day.

In July, 1957, he was noted to have blue lips, and a routine blood count showed a haemoglobin of 93% (13.8 g./100 ml.), the white-cell count was 7,000/c.mm., and Heinz bodies were present in 14% of his

red blood cells. Dapsone was still further reduced, and in November his haemoglobin was 96% (14.1 g./100 ml.) and reticulocytes 1.5%; Heinz bodies were present in 14% of his red blood cells. He then remained well, taking 100 mg. of dapsone once a week, until July, 1958, when he developed erythema multiforme and pneumonia, and had to be admitted to hospital. His dapsone was increased to 100 mg. daily; five days after admission his haemoglobin was 70% (10.4 g./100 ml.), and Heinz bodies were present in 25% of his red cells. Dapsone was reduced and four days later his haemoglobin was 83% (12.3 g./100 ml.), and Heinz bodies were present in 26% of the red blood cells. The reticulocyte level was 4.2%, white-cell count 5,200/c.mm., and blood plasma bilirubin 0.3 mg./100 ml. Two days later he had a cerebrovascular accident; he made a complete and uneventful recovery from this, as well as from his pneumonia and erythema multiforme. At the time of writing he was well apart from hypertension—blood pressure 220/120.

Case 4

This patient, a man of 52, was found to have dermatitis herpetiformis in September, 1956. He was treated by

dapsone, 50 mg. twice daily, which completely controlled his itching and prevented further blister formation. Frequent blood counts showed no anaemia. However, on July 11, 1957, Heinz bodies were found in 8% of his red cells. His haemoglobin at that time was 84% (12.4 g./100 ml.) and his white-cell count 6,100/c.mm. He continued on the same dose of dapsone and remained free from symptoms.

Discussion

The formation of Heinz bodies in the peripheral blood usually indicates chemical poisoning. Fertman and Fertman (1955) list numerous substances which have been shown to cause the formation of Heinz bodies. These include aniline and its derivatives, and nitro-compounds of benzene and toluene; many of these substances are used in industry, and some, particularly the sulphonamides, are of considerable medical importance.

The chemical nature of Heinz bodies, and the mechanism by which they are formed, are not well understood. It is generally agreed that they indicate haemoglobin degradation, and possibly damage to the red-cell stroma in addition. The affected cells have a reduced life-span, and a haemolytic anaemia will develop if the affected cells are eliminated more rapidly than they can be replaced. In this case the Heinz bodies are more numerous, fragmented red cells may be seen in blood films, and the haemoglobin value falls. The anaemia is, in many cases, aggravated by the formation of methaemoglobin or other abnormal pigments.

Moeschlin (1940), in describing the effects of sulphonamides on the red blood cells, thought that if the number of red cells containing Heinz bodies rose above 20% a haemolytic anaemia might develop and the patient should be watched closely. Heinz body levels of over 50% were associated with a frank haemolytic anaemia. The findings in our cases, where the Heinz bodies developed during dapsone therapy, were similar. Thus in Cases 1, 2, and 3 Heinz bodies were numerous, reaching levels of 50%, 40% and 26% respectively. In these cases the haemoglobin had fallen, fragmented cells could be seen in blood films, and reticulocytes were fairly numerous. These findings suggested that a haemolytic anaemia was developing. Case 4 showed small numbers of Heinz bodies (8%) and the drug was continued without the development of anaemia.

It seems that if there are only a small number of Heinz bodies present the haemoglobin will be maintained at a satisfactory level, even if dapsone is continued. If Heinz bodies become more numerous and it is essential to continue treatment a reduction in dosage may be enough to prevent the development of a haemolytic episode. We believe that examination of the blood for Heinz bodies is a valuable procedure in the control of dapsone therapy. It is a simple and rapid test, requiring no special equipment, and can be performed equally well on capillary or venous blood.

Summary

Four cases are described in which blood showed the formation of Heinz bodies following the administration of dapsone.

Three of these patients, whose blood showed numerous Heinz bodies, developed haemolytic anaemia.

Examination for Heinz bodies is a simple and useful test in the control of patients receiving dapsone.

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NYDRANE AS AN ANTICONVULSANT

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During recent years several papers have appeared commenting on the use of "nydrane" as an anticonvulsant drug (Gotten, Hawkes, and Tyrer, 1951; Hawkes, 1952; Merlis and Martin, 1956; Hoenig, Crotty, and Chisholm-Batten, 1956; Robinson, 1957; Sharpe, Dutton, and Mirrey, 1958; and others). Beneficial effects on the convulsive and mental states have been claimed, together with remarkably low toxicity. In the course of routine work in the neurological departments of the General Infirmary at Leeds and Pinderfields Hospital, Wakefield, this drug has been tried in the treatment of epileptics, both in-patient and out-patient. Our results have differed in some respects from those of other workers, and we have thought it worth while reporting our experiences.

The chemical and pharmacological characteristics of nydrane have been widely reported. It differs from all other anticonvulsants in being a benzylamide, and its chemical composition is N-benzyl- β -chloropropionamide. It is found experimentally to protect against artificial convulsions in animals. Its effect is said to be maximal in two hours and to last up to five hours (Harned *et al.*, 1953). It is supplied in 0.5-g. tablets.

Material

Up to the time of writing, 27 patients under the care of Dr. Hugh Garland have been treated with nydrane, either alone or in combination with other drugs. These patients comprise the present series, which is unselected. There were 14 males and 13 females. Their ages ranged from 11 to 55 years. The duration of attacks varied from 2 to 50 years. In general it was poor response to other drugs (barbiturates, hydantoins, and primidone), in combination and in high dosage, which led to the trial of nydrane. Most of these patients responded to some extent to former treatment but continued to have attacks with a frequency of from once monthly to several a day; most were having several weekly. The low toxicity claimed for nydrane led us to try it in two patients with less frequent attacks requiring very high dosage of primidone and phenytoin