In those cases where it has been necessary to hospitalize patients with functional illness, ultimately a decision has to be made concerning the length of stay in hospital. It is obviously impossible to generalize on this point, but it is again necessary to warn against haphazard decisions in this regard. There must be a clinical awareness that the therapeutic benefits of hospitalization might be lost if the patient is discharged prematurely, and similarly, over-hospitalization may be decidedly detrimental to the patient. Provided these aspects of hospitalization are not ignored, clinical errors in this regard are likely to be avoided.

**CONCLUSION**

In the treatment of functional illness, in each case different aspects of the therapeutic programme will assume different degrees of relative importance. If a genuine intellectual honesty is preserved, however, it is frequently extremely difficult to decide whether it has been the drugs, or the psychotherapy, or perhaps some other specific aspect of treatment that has been responsible for a favourable outcome in any particular case.

In attempting to assess the factors that might have been responsible for the success of treatment in any case of functional illness, the role of general principles of management frequently tend to be overlooked. The purpose of this paper has been to draw attention to various aspects of this general management, and to suggest that the course of a functional illness and its response to treatment will depend very largely on the correct application of general management, as distinct from specific forms of treatment.

**SUMMARY**

Comments have been made concerning problems relating to the diagnosis of functional illness. The importance of attempting to make a positive diagnosis of functional illness is stressed. This is followed by a discussion which is intended as a guide towards a satisfactory approach to the general management of functional illness.

**AUTO-IMMUNE HAEMOLYTIC ANAEMIA ASSOCIATED WITH α-METHYLDOPA THERAPY—A CASE REPORT**

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The last decade has seen the introduction of many new hypotensive agents. Of these, α-methyldopa (Aldomet) has enjoyed considerable popularity, possessing as it does several properties that should make it the preferred choice. It has been estimated that in the United Kingdom alone more than 100,000 patients are on continuous treatment with α-methyldopa.

In January 1966, attention was drawn to the possible association between α-methyldopa and the development of auto-immune haemolytic anaemia. At the same time, Carstairs et al. drew attention to the presence of a positive direct Coombs test in about 10% of their hypertensive patients taking α-methyldopa. None of their patients, however, was anaemic. Since then, sporadic reports of auto-immune haemolytic anaemia in patients taking α-methyldopa have appeared in the literature. These and further cases were reviewed by Worlledge et al., giving a total of 30 patients in all. There were 5 fatalities, 2 dying while still anaemic and 3 of vascular accidents after recovery from a haemolytic episode.

This report deals with the findings in a fatal case of auto-immune haemolytic anaemia associated with α-methyldopa therapy. It is, to our knowledge, the first such case to be reported from South Africa and shows some features of particular interest.

**CASE REPORT**

Mrs. R.R., a 50-year-old White housewife from Johannesburg, was admitted to the Johannesburg Hospital on 15 December 1965. She complained of tiredness, giddiness and weakness of 1 month's duration. These symptoms were of gradual onset, with no obvious precipitating factors.

Past history showed that she had been treated for hypertension for several years. Initially, treatment was with reserpine, a thiazide diuretic and guanethidine. Twenty-three months before admission α-methyldopa was added to the regime, in a dose of 750 mg. daily. This was later increased to 1 G daily for a short period and then reduced again to 750 mg. She was taking this latter dose when admitted in December.

In 1959, the patient underwent a partial thyroidectomy for removal of a thyroid adenoma which had been present for 4 years (histology showed a simple Hurthle cell adenoma and pre-operative investigation showed her to be euthyroid). After this she was maintained on thyrogblobulin gr. 2 daily. The patient had no known allergies, and the family history was insignificant.

**Physical Examination**

A middle-aged White female with moderate anaemia but no overt jaundice. The blood pressure was 160/80 mm.Hg; temperature 99.2°F. There were no enlarged lymph nodes or hepatosplenomegaly; the optic fundi showed no haemorrhages or exudates; there were no skin lesions and other systems were normal.

**Investigations**

Haemoglobin 8 G/100 ml., with a haematocrit of 24%; mean cell haemoglobin concentration of 33%; leucocytes 8,600/cu.mm. with a normal differential count; reticulocyte count 40%; ESR 3 mm. in the first hour (Wintrobe). Peripheral blood films showed the presence of occasional Howell-Jolly bodies in the erythrocytes. Wet platelet count 280,000/cu.mm.; blood urea 28 mg./100 ml.; total serum bilirubin 4.8 mg./100 ml. (unconjugated 4.4 mg./100 ml.); urinary urobilin present in marked excess; urinary bilirubin absent; faecal stercobilin present in marked excess; direct Coombs test strongly positive (21
December 1965; Schumm's test negative; latex antinuclear protein test for lupus erythematosis negative on repeated occasions; tanned red-cell and agar gel precipitin test for thyroid auto-antibodies negative; VDRL negative; serum vitamin B12 250 μg./ml. (normal 250 - 1,100 μg./ml.); serum folic acid 21 μg./ml. (normal 3 - 15 μg./ml.); serum iron 94 μg./100 ml.; lactic dehydrogenase 400 units. A 51Cr-red-cell survival study, injecting the patient's own labelled cells, showed a mean cell life of 66 days (normal 100 - 130 days). Chest X-ray showed an unfolded aorta but clear lung fields.

Course

Because of the possibility that the haemolytic anaemia represented a complication of α-methyldopa therapy, the drug was withdrawn from the patient's therapeutic regime soon after admission. It was decided further to try the effects of steroid therapy in arresting the haemolytic process and 1 week after admission prednisone was commenced with a dose of 60 mg. per day. The blood picture began to show progressive improvement and the dose of prednisone was gradually reduced (Fig. 1). Nine weeks after commencement of therapy the haemoglobin level had risen to 13.5 G./100 ml. and the patient was discharged, feeling quite well. The dose of prednisone was reduced to 5 mg. per day and it was stopped completely 2 weeks later. Alpha-methyldopa was not restarted. The patient was seen at regular intervals thereafter. Her blood pressure was reasonably well controlled with guanethidine and hydralazine, and repeated blood counts remained normal. Repeated direct Coombs tests were unfortunately not done.

On 27 September 1966 she was readmitted to hospital with a 2-week history of malaise, listlessness and fever. As far as could be ascertained, she had not been surreptitiously taking α-methyldopa again. Physical examination showed her to be severely anaemic and moderately jaundiced, with a pyrexia of 99.4°F. Blood pressure was 140/90 mm. Hg. Investigations indicated a flare-up of the auto-immune haemolytic anaemia (haemoglobin 6.2 G./100 ml.; reticulocytes 17%; serum bilirubin 5.7 mg./100 ml.—unconjugated 4.8 mg./100 ml.; Schumm's test positive) with a direct Coombs test again strongly positive. Blood urea was 39 mg./100 ml. A sternal marrow aspirate showed a hypercellular marrow with erythroid hyperplasia; slight megaloblastoid changes were noted. Steroid therapy was recommenced the following day. Within 24 hours, however, the patient exhibited a violent haemolytic crisis (haemoglobin 4.4 G./100 ml.), and she died 2 days later, despite intensive supportive therapy. Permission for an autopsy was not obtained.

DISCUSSION

Many of the features shown by this patient were similar to those described by other authors, viz. the insidious development of haemolytic anaemia after having been treated for hypertension with α-methyldopa for several months; the finding of a strongly positive direct Coombs test; the reduced survival of 51Cr-labelled erythrocytes in the patient's circulation; the initial fairly rapid improvement following withdrawal of the drug and steroid therapy, and the failure to find any other cause for the acquired haemolytic process. The fact that the red-cell survival time was not more strikingly reduced is probably explained by the commencement of steroid therapy before the test was started or by the labelling of a new population of erythrocytes. The reduced serum folate level found in the first admission has been reported in patients with haemolytic anaemia and probably reflected excessive demand for folate acid.

Only 3 previously reported cases developed a recurrence of haemolysis when steroid therapy was reduced or stopped. These were all patients in whom α-methyldopa therapy was reinstated. In one of the cases, described by Hamilton et al., there was a recurrence of haemolysis 3 months after cessation of steroids; in the other cases the time interval between relapses was not precisely documented. One other report indicated the haemolytic syndrome to be still active 6 weeks after withdrawing α-methyldopa. The time interval between the two episodes of haemolysis in our patient was 7 months. It would have been of considerable interest to know whether the direct anti-globulin test remained positive during the 7 months when she was asymptomatic. Unfortunately this was not recorded. However, it probably remained positive, since the first negative Coombs test observed in the series of Worlledge et al. only occurred 7 months after stopping α-methyldopa.
The main significance of this case lies in the recurrence of anaemia after the patient had kept relatively well and was off \( \alpha \)-methyldopa for several months. There was no clinical or laboratory evidence to suggest that another disease process had developed in the interim. It is possible that maintenance steroid therapy after discharge in February would have averted the second, fatal crisis. We therefore recommend that any patient who develops an auto-immune haemolytic anaemia in association with \( \alpha \)-methyldopa therapy should be carefully watched for several months thereafter and probably be kept on prolonged steroid administration—at least until the Coombs test becomes negative.

Alpha-methyldopa is not the only drug which may result in the development of a Coombs-positive auto-immune haemolytic anaemia. Petz and Fudenberg\(^{22} \) described a similar situation following large-dosage penicillin administration, while fuadin,\(^{18} \) phenacetin and PAS\(^{24} \) have all been implicated. A careful drug history would therefore appear to be of importance in any patient presenting with auto-immune haemolysis.

In view of widespread use of \( \alpha \)-methyldopa in South Africa, it will be of interest to see if further cases come to light.

**SUMMARY**

A 50-year-old White female presented with a short history of tiredness, giddiness and weakness. She had been treated for alcoholism, which was noted to cause stress, anxiety and weakness. She had been treated with Esucos for several months before admission. Investigations showed the presence of a Coombs-positive auto-immune haemolytic anaemia. Red-cell survival studies showed the mean cell life to be reduced. There was a fairly rapid improvement following withdrawal of \( \alpha \)-methyldopa and institution of steroid therapy. However, 7 months later the patient had a fatal haemolytic crisis. Attention is drawn to the association between \( \alpha \)-methyldopa and the development of an auto-immune haemolytic anaemia. It is recommended that such patients be carefully watched for several months thereafter and probably be kept on prolonged steroid administration.

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**REFERENCES**


**DIXYRAZINE (ESUCOS) IN DIE BEHANDELING VAN AKUTE ALKOHOLISME**

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By die behandeling van die akute onttrekkingsimptome na die inname van groot hoeveelhede alkohol, speel fenotia-derivate 'n belangrike rol. Hierdie middels is veral doeltreffend vir:

(a) Die potensiëring van die sederende effek van die alkohol, al eers in die pasiënt se sisteem teenwoordig, wat sodoende 'n sterk kalmerende effek tot stand bring sonder enige rusteloos (geagiteerde) depressie soos wat dikwels na barbituraat-toediening gesien word.

(b) Die kontrole van die neiging om te braak. 'n Vin­niger herstel van vog-, elektroliet- en voedingsbalans word in die hand gewerk.

(c) Die verligting van angs.

Potensieel-verslawende middels word liefst geheel en al vermy. Die dosis paraaldehiede of fenobarbitoon wat bv. die meeste mense sou kalmere, maak die alkoholis dikwels juist opgewonde en moeilik om te hanteer. Die dosis van hierdie middels, groot genoeg om die alkoholis te kalmere, lê na aan 'n gevaarlike hoogte en lei tot onttrekkingsim­ptome.

In hierdie ondersoek is die terapeutiese waarde van 'n fenotia-derivaat, dixyrazine (Esucos), by akute sim­tome van alkohol-onttrekking nagegaan. Esucos word be­skryf as 'n neuroleptiese middel met sederende en angs­opheffende eienskappe. Dit besit ook 'n matige anti­depressiewe effek. Die chemiese struktuur vertoon 'n kern van psigomotoriese opgewondeheid die in name van groot hoeveelhede alkohol, speel fenotiaziderivaties 'n belangrike rol. Hierdie middels is veral doeltreffend vir:

1. Eersfaase (lau dosering)
3. By opname het al die pasiënte Esucos ontvang in dosisse in gevalle met psigomotoriese opgewondenheid. Dit is gebruik in gevalle van senusoorienteerde of pre-koma en hoër dosisse in gevalle met psigomotoriseerde opgewondenheid.