3. No abnormality found on clinical and haematological examination. Osmotic fragility of red cells within normal limits. Foetal haemoglobin 2% of total.

4. No abnormality on clinical and haematological examination. Osmotic fragility of red cells was within normal limits. Foetal haemoglobin less than 2% of total.

5. Case 1, described.

6 and 7. No haemoglobin-H found on paper electrophoresis. Foetal haemoglobin less than 2% of total.

Paper electrophoresis did not show any increase of HbA₂ in any of the relatives of Case 1.

The Family of Case 2

1. Paper electrophoresis showed no haemoglobin-H. Haemoglobin 8.9 g./100 ml. This anaemia responded to the administration of iron, her haemoglobin rising to 12 g./100 ml. Foetal haemoglobin 2% of total.

2. Not examined.

3. Electrophoresis showed haemoglobins A and H. She was suffering from a mild anaemia, similar to Case 2; haemoglobin 10.4 g./100 ml. Occasional target cells seen in blood film. Foetal haemoglobin less than 2% of total.

4. Case 2, described.

5. Not examined.

6. Paper electrophoresis showed no haemoglobin-H. Foetal haemoglobin less than 2% of total.

7. Paper electrophoresis showed no haemoglobin-H. Foetal haemoglobin 5% of total. (Child aged 1½ years; haemoglobin 13 g./100 ml.; normal red cell fragility.)

Paper electrophoresis did not show any increase of HbA₂ in any of the relatives of Case 2.

FIG. 3.—Family tree of Case 1.

FIG. 4.—Family tree of Case 2.

Discussion

The results described show that haemoglobin-H disease is characterized by a slight reduction in the life span of red cells which is not associated with splenic destruction. There is a decrease in marrow activity, which is compensated for by marrow extension, and this results in a slight increase in total red cell output. Output, however, does not compensate completely for haemolysis. The life span of red cells appears to be variable, as a patient who at one time showed clear evidence of haemolysis later had an almost normal cell survival. These findings are similar to those in thalassaemia (Bailey and Pranker, 1958), which the disease closely resembles in clinical features and haematological findings. However, it differs from thalassaemia minor in that HbA₂ is not increased in the patients or their relatives (Vella, Wells, Ager, and Lehmann, 1958). The cases so far reported have been from races in which thalassaemia occurs (Vella *et al.*, 1958); and Motulsky (1956) states that haemoglobin-H disease is the result of the interaction of the thalassaemia and "H" genes. Our two families show no evidence to support this theory, as none of the relatives have thalassaemia.

Summary

Four cases of haemoglobin-H disease are reported from two Greek Cypriot families living in London. One case from each family has been studied in detail, and results of red cell survival time and marrow iron turnover are presented. The familial nature of the disease is demonstrated.

We are grateful to Dr. E. A. Blake Pritchard for permission to study and publish Case 1.

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TOXIC PSYCHOSIS FOLLOWING ATROPINE EYE-DROPS

BY

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AND

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It is well known that atropine may produce a delirium in addition to its more characteristic autonomic effects, and that in certain sensitive subjects these effects will arise with normal pharmacological doses. It is less well known that atropine can produce delirious states with minor or absent peripheral signs of intoxication and that severe mental reactions can follow routine instillation of atropine eye-drops.

The case described is one of acute toxic psychosis caused by routine atropinization of the right eye over a period of three and a half weeks in the course of treatment of retinal detachment.

The condition is rare in adults and few cases have been reported in the literature (Hopkins and Robyns-Jones, 1937; Listwan and Whealy, 1953; Schinko, 1954), but it is suggested that milder degrees of mental disturbance often seen after eye surgery and attributed to emotional stress of the post-operative regime may be due in part to atropine intoxication.

Case Report

The patient was a married woman of 33, without children, intelligent, and described by her family as somewhat highly strung, emotional, and imaginative. After the death of her father two years ago she had spent three days in a neurosis unit, the diagnosis being reactive depression with hysterical features. There was a similar episode 11 years ago after the death of her first husband, but without admission to hospital.

The medical history included rheumatic fever at the age of 12, followed by a slight persistent tachycardia, and myopia requiring 10 dioptries correction. She had recently worn contact lenses. There was no significant family history.

On June 29, 1957, she was admitted to Moorfields Annexe, Highgate, with a right temporal retinal detachment. Treatment with bed rest, double eye pads, and daily instillations of 1% atropine sulphate drops was instituted. On July 4 she was transferred to Moorfields Hospital, where the atropine drops were instilled twice daily. At this time she was judged to be "unstable in temperament," and phenobarbitone, ½ gr. (32 mg.) t.d.s., was added to her treatment.

Diathermy and subretinal aspiration was performed on July 8 under thiopentone, gallamine triethiodide, gas and oxygen, with premedication by "omnopon" and scopolamine. There were no complications. Atropine drops twice daily, eye pads, and strict bed rest were continued until July 19, when masked glasses were substituted for the pads,

more liberty of movement was allowed in bed, and the phenobarbitone was replaced by chlorpromazine, 25 mg. t.d.s.

Over the next four days she became increasingly noisy, disorientated, and irrational, and required oral and intramuscular barbiturates. By July 23 she was quite unmanageable and was transferred to Three Counties Hospital on an Urgency Order.

On admission she was disorientated in time and place, was amnesic for recent events, mistook identities, and asked if she was to have an operation. She was restless and garrulous, refused to stay in bed, called out in terror, and at times wept uncontrollably. She stated that she had seen the Cross and "boats to sail away in," and had heard the voices of near relatives. She believed people to be talking about her and plotting against her. At times she showed partial insight.

On examination she was of average physique; the right pupil was fully dilated and the left less so and reacting to light; the gait was slightly ataxic; there was a tachycardia of 150 a minute, and the blood pressure was 170/90. There were no other abnormal physical findings.

Next day her mental state had deteriorated. She was resistive and hostile, offered violence, was incontinent, and refused food. This state was not continuous, but was broken by more lucid intervals, during one of which she was sufficiently quiet for an E.C.G. tracing to be taken. This showed (first tracing in Figure) a regular sinus tachycardia,

E.C.G. Lead V₁. (1) On admission (July 24). (2) At 11 a.m. on August 13. (3) At 3.45 p.m. on August 13—atropine sulphate, 1/66 gr. (1 mg.), given at 11.10 a.m. (4) At 6.45 p.m. on August 13—neostigmine, 1 mg., given at 4 p.m.

rate 130, with diphasic T wave throughout the chest leads and some elevation of the ST segment. The white-cell count was 15,000, with a polymorphonuclear leucocytosis; Hb, 102%; W.R. negative; E.S.R. 7 mm./hr.; urine, N.A.D.; chest x-ray examination N.A.D.

At this stage the diagnosis lay between an acute schizophrenic reaction and a toxic delirium, the latter being more probable because of the lucid intervals, visual hallucinations, and disorientation, together with the myocardial findings. It was tentatively suggested that the condition might be due to atropine poisoning, but this was discounted by outside medical opinion; for fear of neglecting the post-operative care of the eye the drops were continued.

By July 25, despite sedation, her mental condition had deteriorated further and tube feeding had to be instituted. Electroplexy was considered, but thought to be too dangerous in view of the toxic state of the myocardium. The pulse rate remained at approximately 150. It was decided to discontinue atropine, and within 24 hours there was some improvement in her mental state.

After 48 hours the pulse rate had fallen to 96, but mentally she was relapsing again and refusing nourishment. It was now thought that her myocardial condition had improved enough to allow electroplexy, which was indicated by her continued overactivity, resistiveness, and refusal to take nourishment. Daily E.C.T. was given until July 30, by which time she had greatly improved, was normal in behaviour and mood, and had no disturbance of cognitive function. Over the next few days, however, she again became more

labile emotionally, rather demanding and querulous, and was expressing paranoid ideas.

By August 6 she had gained in insight and was more settled, but still emotionally unstable and liable to tears. On the 8th a suture was removed from the eye by our visiting ophthalmic surgeon and a satisfactory report given on the state of the retina. An E.C.G. tracing taken on August 9 was within normal limits, rate 96.

In view of the possibility that this patient might need further treatment to her eyes in the future, it was considered important to assess the part played by atropine in the aetiology of her psychosis, so on August 9 an injection of atropine sulphate, 1/100 gr. (0.65 mg.) was given subcutaneously, with the suggestion that it was a sedative. Six hours later she developed a garrulous, emotional, paranoid, hallucinated state resembling in lesser degree her condition of the previous week. Systemic effects were negligible. Unfortunately she was too uncooperative to permit a further E.C.G. being taken. Next morning she was more settled, but still showed some pressure of ideas and a tendency to form illusions.

In order to eliminate the possibility that this was a chance relapse, and if possible to have electrocardiographic confirmation of the effects of atropine, a further trial dose of the drug, this time 1/66 gr. (1 mg.), was given subcutaneously at 11.10 a.m. on August 13, again with the suggestion that it was a sedative. An E.C.G. was taken (second tracing in Figure) 10 minutes before the injection and was normal, rate 96. By midday she showed pressure of ideas and increased lability of affect, but no significant systemic effects or alteration of the pulse rate. By 2 p.m. she complained of a burning sensation in the palms of her hands and in her brain, and said she felt she could no longer contain herself or suppress her feelings. She began to make absurd accusations against the hospital and demanded her immediate discharge on the grounds that her room was a locked cell (untrue) and that the tea was not strong enough. She asserted that patients were being given nicotine injections to make them cough, and that others were being gassed. She could smell the gas (not true) and insisted that she could hear men laughing, her sister's voice, and the click of billiard balls. Visual hallucinations were also suspected.

An E.C.G. taken at 3.45 p.m. (third tracing in Figure) showed the same slight elevation of the ST segment and diphasic T wave as in the tracing taken on admission (first tracing in Figure). There was no increase in sinus rate.

At 4 p.m. 1 mg. of neostigmine was given, and a further E.C.G. taken at 6.45 p.m. (tracing 4 in Figure) showed that the myocardial changes produced by the atropine had resolved. Her mental condition, however, did not settle markedly until next morning, and not completely until three days later.

She was discharged on August 16, and has since remained well and has returned to work.

Discussion

Listwan and Whealy (1953) described the characteristic mental symptoms of atropine intoxication as a confusional state with vivid visual hallucinations, restlessness, muscular incoordination, and later increased emotionalism with a short period of retrograde amnesia. In our case all these features were present together with aural and olfactory hallucinations. Peripheral post-ganglionic cholinergic effects were minimal apart from the tachycardia on admission. It is thought that the E.C.G. changes were due to direct action on the myocardium, as in the model psychosis there was no increase in sinus rate.

Fleury and Marx (1949) pointed out that intoxication is not due to transconjunctival absorption but to the swallowing of atropine-laden tears. In 1% atropine sulphate, each drop contains 1/110 gr. (0.6 mg.). Assuming complete absorption, three drops in the normal subject will produce parasympathetic paralysis, six drops restlessness, and 15 drops mental symptoms and ataxia. In sensitive subjects

mental or peripheral symptoms will follow much smaller doses. Children (Tyson, 1889; Kelynack, 1890; Scally, 1936; Duggan, 1937; Belz, 1949; Fleury and Marx, 1949) and the elderly (Métivier, 1935) are particularly affected.

Recommendations to reduce the risk of side-effects from atropinization of the eye have included the use of a 0.5% solution, precautions to avoid concentration of the solution by evaporation, and compression of the internal angle of the eye to obstruct the lacrimal duct during instillation (Belz, 1949; Fleury and Marx, 1949).

It would be interesting to know if any positive correlation could be found between the more minor emotional disturbances and restlessness which often accompany eye surgery, and any particular dosage or method of atropine administration.

Summary

A case is described in which an acute confusional psychosis resulted from the routine administration of 1% atropine sulphate drops in the treatment of retinal detachment. The psychosis was accompanied by myocardial changes giving rise to considerable concern. Other peripheral signs of atropine intoxication were absent. A remission of the confusional state followed discontinuation of the eye-drops and a short course of electroplexy; paranoid trends and emotional lability persisted for a further few days.

At a later date, in order to establish a diagnosis, small test doses of atropine were given by injection. Both the psychotic symptoms and the myocardial change seen when the patient was having atropine eye-drops were reproduced.

The literature concerning mental symptoms following the use of atropine eye-drops is reviewed and possible preventive measures against intoxication are described.

It is suggested that closer investigation might be made into the origin of states of minor emotional disturbance, usually attributed to psychological stress, in patients undergoing eye surgery with prolonged routine atropinization. E.C.G. changes appear to be useful in establishing a diagnosis of atropine sensitivity where other peripheral signs of intoxication are lacking.

Our thanks are due to Dr. Leslie Ford, medical superintendent of Three Counties Hospital, for permission to publish this case, to Dr. L. G. M. Page, deputy medical superintendent, for his help and advice, and to Dr. D. W. Hill for details of treatment at Moorfields Eye Hospital.

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Opening a conference on cerebral palsy, held in London on November 21 by the British Council for the Welfare of Spastics, Mr. R. H. M. THOMPSON, Parliamentary Secretary to the Ministry of Health, said that the overall needs of children and young people suffering from cerebral palsy were early ascertainment, full assessment, expert treatment, education, training for future employment, and continuing aftercare in the community. At the same time the parents needed guidance in the child's home management, and help in coping with their own numerous practical and personal problems. The need was to build up a system of comprehensive care available to sufferers throughout their lives. Mr. Thompson thought the greatest need was for further understanding of the causation of the disease, for it was only in this way that we could prevent it. Research into its causation and treatment would ultimately be of benefit to children suffering from other handicaps also.

RENAL COLIC AND ANURIA FROM ACETAZOLAMIDE

BY

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Acetazolamide, "diamox," is a sulphonamide derivative and inactivates carbonic anhydrase. By oral administration it is rapidly absorbed, and is excreted largely unchanged by the kidney within 6-12 hours. The inhibition of carbonic anhydrase leads to increase of sodium bicarbonate in the urine and increased potassium output.

Acetazolamide is widely used for glaucoma and as a diuretic in cardiac disease, and is reputedly very free from serious complications; only three papers have appeared in America reporting complications and none at all in Great Britain, which is the reason for the publication of this case.

Case Report

The patient, a man aged 54, was quite well until 5:30 p.m. on May 1, 1958, when he passed urine normally. Shortly afterwards urgency developed and a quantity of "very thick urine" was passed with pain. Pain then developed in the right loin; it radiated to the groin and was associated with frequency, penile pain, and haematuria. He was seen by Dr. J. Williams, who diagnosed renal colic.

Next day the patient voided 15 oz. (425 ml.) of clear urine in the morning and complained only of a dull ache in the right loin. Later, severe low back pain developed with left-sided abdominal pain and vomiting.

On May 3 the severe low back pain and vomiting continued and no urine was passed for 24 hours. The patient was admitted to Leatherhead Hospital; temperature 99° F. (37.2° C.). No stones were seen by straight radiograph. Cystoscopy (lignocaine gel analgesia) showed the bladder to be empty but otherwise normal. The right ureter was inactive and a catheter could not be passed beyond 1 cm. The left ureter was obstructed at 5 cm., but a catheter with stylet was successfully forced through and bloody urine poured down the ureteric catheter under considerable pressure.

The ureteric catheter was tied in and 38 oz. (1,077 ml.) drained through it during the night. Distaquaine penicillin, 300,000 units, was given daily for six days from May 3. Sulphonamide crystalluria was diagnosed, and sodium bicarbonate, 60 gr. (4 g.) 4-hourly, was given orally and intravenous saline discontinued early, as the patient took well by mouth.

On May 4 the blood urea was 95 mg. per 100 ml.; plasma CO₂, 16.1 mEq/l.; serum chlorides, 106 mEq/l.; sodium, 139 mEq/l.; potassium, 4.6 mEq/l. Urine: bladder and left ureter, sterile; red cells ++; no crystals.

Progress was satisfactory; urine drained well from the ureteric catheter and the left renal pain was relieved at once. After about 12 hours the patient voided a few ounces of urine around the catheter; this was thought to be from the right kidney, as relief of right renal pain then occurred. The blood pressure was 150/85. The ureteric catheter was removed on May 6 after retrograde pyelography had shown a curious beaded appearance at the lower end of the ureter which might have been due to oedema or collections of crystals. The blood urea had fallen to 72 mg./100 ml.

The following day the patient was passing clear urine, but a peak of temperature followed, due to pyocyanus infection of the urine, which responded well to a five-day course of chloramphenicol.

On May 18 the patient was discharged well with a blood urea of 29 mg./100 ml.