diagnosis, but, in the absence of such assistance, one or other of the following diseases might have entered into the differential diagnosis.

1. The combination of respiratory distress with tachycardia has to be differentiated from the dyspnoea of cardiac or respiratory origin. The absence of cyanosis and of abnormal clinical signs in the chest should serve to exclude any thoracic disease, though the presence of pyrexia might at first suggest the possibility of some infective illness.

2. The association of hyperpnoea with the presence in the urine both of acetone and of a reducing substance resembles a ketosis of diabetic origin, but the latter diagnosis is eliminated by the ferric chloride test for aspirin and by the yeast fermentation test, which demonstrates that the main reducing substance is not glucose. The diagnosis can be confirmed, if necessary, by a blood-sugar estimation.

3. Dyspnoea and signs of kidney damage also occur in renal asthma, but the absence of other signs of uraemia, together with the presence of aspirin and salicylic acid in the urine, should readily differentiate the two conditions.

4. The mental symptoms, pyrexia, and respiratory disturbance may simulate a form of infective encephalitis, but the specific urine tests should clinch the diagnosis.

Treatment

The main principles of treatment in this case were as follows:

Elimination of the Poison.—(a) Gastric lavage was performed with sodium bicarbonate 1 dr. in one pint of water, after which about 5 oz. of the solution was left in the stomach. As the patient was not seen until 14 hours after taking the drug it is doubtful if this treatment can have been of much benefit. (b) She was given aperients. (c) She was encouraged to take as much fluid as possible, in order to hasten excretion of the drug by kidneys and skin.

Neutralization of the Acidosis.—Sodium bicarbonate 30 gr. was administered every two hours.

Abolition of the Ketosis and Treatment of the Toxic Hepatitis by Insulin and Glucose Therapy.—The treatment was begun on the second day with an injection of 40 units of insulin, combined with oral administration of 40 g. of glucose. This was followed by 20 g. of glucose every two hours for 12 hours. She was then given injections of 10 units of insulin morning and evening half an hour before meals, followed in each case by 40 g. of glucose three hours later.

A diet of high carbohydrate (with low protein and fat) content, in order to assist recovery from the hepatic damage and to avoid further strain on the kidneys.

Lumbar puncture was not performed, but a perusal of the literature reveals that Dyke (1935) and Neale (1936) record cases of benefit from this treatment, the former also reporting a purple colour on the addition of iron perchloride to the cerebrospinal fluid.

Commentary

Clinical Signs.—(1) There was a latent period of about 14 hours between the taking of the drug and the onset of severe toxic signs. This phenomenon has also been observed by Neale and by Biddle (1938). (2) The patient suffered from a mild pyrexia, which appears to be a common symptom, having been recorded by Neale and by Dyke. (3) The most characteristic sign was her marked hyperpnoea, associated with a strongly acid urine. It was caused by acidosis, presumably resulting from (a) the direct action of the acid radical of the acetylsalicylic acid, and (b) disordered metabolism, as exemplified by the acetone in her urine. The difference of opinion over the relative importance of these two factors has been discussed by Dyke, who points out that, whereas Quincke attributes the hyperpnoea to the direct action of the drug, Balázs considers that the sign occurs only in the presence of acetone in the urine. (4) Another feature was disorientation, which might be expected to occur in an organic reaction type of mental disorder. With the exception of drowsiness, no other mental abnormality was present, but symptoms such as restlessness, delirium, and terminal convulsions have been reported by several writers. (5) That the poison caused a toxic hepatitis was shown by the hepatomegaly and by the presence in the urine of bile, acetone, and a trace of glucose. There was no jaundice. (6) There was also evidence of toxic damage to the kidneys; for, as stated above, the urine contained albumin, blood, and pus cells. (7) The oliguria—a symptom also noted by Andrews (1938)—was probably secondary to the excessive perspiration. There was no evidence of dehydration, though this sign has been observed by Neale, Biddle, and Dyke.

Course.—A study of the table of progress will show that there was considerable delay in complete excretion of the

aspirin, the iron perchloride reaction being still slightly positive four days after the taking of the drug. Recovery after such a large dose of aspirin as 750 gr. must be uncommon. Neale (1936) records two fatalities after 200 gr. and 750 gr.* respectively, and Biddle (1938) cites a case of death after 500 gr. Evans (1938) describes a case of recovery after a dose of 1,500 gr., but his account suggests that he reached the patient soon enough to be able to hinder absorption by inducing prompt emesis, followed by gastric lavage.

I am indebted to Brigadier E. A. Sutton, Director of Medical Services, G.H.Q., East Africa Command, for permission to publish this article.

REFERENCES

- Andrews, M. C. (1938). *British Medical Journal*, 2, 106.
Biddle, E. (1938). *Ibid.*, 1, 1365.
Dyke, S. C. (1935). *Lancet*, 2, 613.
Evans, G. S. W. (1938). *British Medical Journal*, 2, 386.
Neale, A. V. (1936). *Ibid.*, 1, 109.

PROSTIGMIN IN THE TREATMENT OF DELAYED PERIOD

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From 1940 several papers have been published in America and by workers from the Continent (Hechter *et al.*, 1940; Soskin *et al.*, 1940; Winkelstein, 1942; Carapetyan, 1943) on the action of prostigmin on delayed period; and although the results seem very promising no reports have as yet appeared in this country. This drug, made by Roche Products Ltd., has been given an extended trial at the Royal Free Hospital, and its effects on 90 patients are recorded below. It is claimed by those workers that prostigmin invariably precipitates the menstrual flow in all cases of recently delayed period not due to endocrine dysfunction, systemic disorders, or pregnancy. Their second claim, that it is consequently an alternative to the Friedman test with regard to its accuracy, is not dealt with in the present paper.

Mode of Action

According to the above-mentioned workers, "hyperaemia is probably an important and constant factor in menstrual bleeding." This hyperaemia (a) is a result of oestrogenic action on the uterus, and coincides with the property of the hormone of liberating acetylcholine (Reynolds, 1939), thus producing vasodilatation; and (b) is under the influence of the parasympathetic nervous system. This being so, it is easy to understand why physical, mental, and emotional upsets, and causes still undiscovered, by altering the parasympathetic control, give rise to a non-endocrine form of amenorrhoea in about 60% of cases. Coincident with this the diminished formation of acetylcholine within the uterine tissues causes a lack of vascular response. This deficiency could be rectified by the administration either of acetylcholine itself or, better still, of a chemical agent such as prostigmin which potentiates the naturally occurring acetylcholine in the uterine endometrium by inhibiting acetylcholinesterase, as in the treatment of myasthenia gravis. It is thus possible to produce hyperaemia similar to that following oestrogenic action without the ill effects which may result from the further addition of acetylcholine (Perlow, 1939).

Description of Treatment

Choice of Patients.—"Unsuitable patients" were those with obvious endocrine disturbances, a history of long-standing amenorrhoea, or obvious menopausal symptoms though the menstrual delay was relatively short. Nine such patients were treated without success, and were not included in our series of 90 cases. The ages of the patients varied from 16 to 47 years and the duration of amenorrhoea beyond expected menstruation from 3 to 47 days. Out of the 90 recorded cases 30 either were known to be pregnant before treatment began or were later found pregnant on clinical or biological investigation. They were therefore not expected to respond to treatment, which in no case caused bleeding to occur.

* The dose mentioned is 150 tablets, but it is assumed that each tablet contained 5 gr. of aspirin.

Technique.—The routine adopted for patients with previously normal or only slightly irregular menstrual histories consisted of one intramuscular injection of 1 mg. of prostigmin on three successive days, this treatment being discontinued if after the first or second injection the menstrual flow was restored. With the exception of two cases which failed to respond, the longest interval between the last injection and the onset of menstruation was about 72 hours. These periods were normal in quantity and duration, and in two cases biopsy proved the flow to be of a truly menstrual character.

Table of Results

Group	No. of Cases	Bleeding Occurred
1	30	Nil
2	24	82.8%
3	36	94.5%
Control ..	10	Nil

Group 1: Pregnant patients.
Group 2: Poorly selected cases; $\frac{1}{2}$ -mg. doses of prostigmin injected, only occasionally 1 mg.
Group 3: Properly selected cases; 1-mg. doses given from the beginning.
Controls: Out of Groups 2 and 3; sterile water injected.

Illustrative Case.—A 2-para. Has always had regular periods, and presented herself in March and April with a delay of three days each time. She was treated with prostigmin. After one injection of 1 mg. on each occasion a normal period started. In August she had a delay of 8 days. Two full courses of prostigmin at an interval of 8 days had no effect. An A.-Z. test was returned positive, and later the pregnancy was confirmed clinically.

Complications

A number of patients complained of frequency of micturition and giddiness. One woman with a menstrual delay of 8 days complained, 20 minutes after the second injection of 1 mg., of "a film before my eyes, strong palpitations, sickness, and a terrific rush of water which came out of my mouth." She rapidly recovered from the attack without treatment. The action of prostigmin on the salivary secretion may conceivably have been the cause of some of these symptoms (Wright, 1940). This was the only really unpleasant incident in the series.

Conclusions

It appears that the age of the patient and the length of the menstrual delay are not decisive points in selecting the cases; some observers have reported successful treatment in patients with a delay up to 52 days. The character of the previous menstrual cycle, which should have been quite regular or have shown only slight variations, is of greater importance. Prostigmin is reliable in its action, as is shown by its success in 94.5% of this series. One wonders whether the two failures may not have responded to a fourth injection or to slightly larger doses. The drug causes some minor discomfort of a transient and not serious character, but it is quite safe and pregnancy is not disturbed.

The type of patient we had to deal with raises the question whether a wait-and-see policy or any other "psychological treatment" may not have been followed by similar success in a considerable percentage of cases. The injection of sterile water in 10 cases, previous to the proper prostigmin course, gave entirely negative results. Even if it were true that in cases of "functional amenorrhoea" the period will appear sooner or later with rest, tonics, etc., it should be borne in mind that prolonged amenorrhoea may lead to atrophic changes in the uterine muscle. The results are encouraging, and prostigmin deserves further clinical trial. We would suggest that the drug should be tried in all cases of delayed period except those of endocrine origin and those in which pregnancy has been established. Further clinical work may also reveal interesting effects of prostigmin in cases of dysmenorrhoea.

Summary

Ninety cases of amenorrhoea were treated with prostigmin. From 1 to 3 injections of 1 mg. were given.

The results obtained were favourable: in 94.5% of the cases of delayed period not due to pregnancy the menstrual flow was restored.

Prostigmin is safe; from its use no serious ill effects were observed. There is no tendency of the drug to interfere with the course of pregnancy.

This treatment should be reserved for cases with a previously regular or only slightly irregular menstrual cycle.

I wish to thank Miss G. Dearnley, honorary gynaecologist of the hospital, for allowing me access to her cases.

REFERENCES

- Carapetyan, H. (1943). *J. Amer. med. Ass.*, **122**, 81.
Hechter, Oscar, Lev, Maurice, and Soskin, Samuel (1940). *Endocrinology*, **26**, 73.
Perlow, Samuel (1939). *J. Pharmacol.*, **66**, 66.
Reynolds, R. S. M. (1939). *J. Physiol.*, **95**, 258.
Soskin, S., Wachtel, H., and Hechter, O. (1940). *J. Amer. med. Ass.*, **114**, 2090.
Winkelstein, L. B. (1942). *Amer. J. Obstet. Gynec.*, **44**, 231.
Wright, Samson (1940). *Applied Physiology*, London.

Medical Memoranda

A Case of Dysentery associated with *Bact. alcalescens*

The following case may be considered of interest seeing that only in the last few years has *Bact. alcalescens* been recognized as an organism capable of producing acute dysentery. Nabarro and Edward's (1939) paper on this subject has induced us to regard the case as worthy of record.

CASE RECORD

Mrs. M., a nursing sister aged 25, was admitted to hospital on Sept. 9, 1941, with a history of intermittent diarrhoea for six weeks. After admission her stools presented typical dysenteriform appearances, and she was given appropriate medicinal and dietetic treatment. At no time was she acutely ill, nor did she have much pain. Under treatment she improved, but blood and mucus in small amounts persisted in the stools for some weeks. On Sept. 9 her stool, submitted before admission, consisted of gross blood-clot without visible faecal matter; it was cultured on two Wilson and Blair plates and tetrathionate broth (paratyphoid infection was suspected), also on two MacConkey plates. The Wilson and Blair plates proved to be entirely negative. Both MacConkey plates were covered by a profuse growth of non-lactose-fermenter with a few colonies of *B. coli*. The non-lactose-fermenting organism was identified from its cultural and fermentative reactions by the E.M.S. Laboratories as *Bact. alcalescens*, but was not agglutinated by either of the two sera available for this organism in the National Collection. Stools examined on Sept. 28 and Oct. 10 and 18 all contained small quantities of blood-stained mucus, and all, on culture on MacConkey plates, gave a heavily preponderant growth of *Bact. alcalescens* with only a few colonies of *B. coli* and *B. lactis aerogenes*. Serum examined on two occasions showed no agglutinins for the typhoid-paratyphoid group. Serum obtained on Oct. 18 showed no agglutinins for the patient's own strain of *Bact. alcalescens*. This was confirmed by the E.M.S. laboratories, which also tested for agglutinins for all the available strains of dysentery bacilli, with a negative result.

From Nov. 4 a live broth culture of *B. acidophilus* was administered daily for a fortnight. A stool examined on Nov. 8 contained no blood or mucus, and gave a negative result to tests for occult blood, and on culture showed only *B. coli* and *B. lactis aerogenes*. A stool examined on Nov. 21 contained no blood or mucus, but on culture a small number of *Bact. alcalescens* were found, with numerous *B. coli*. As the patient was now free from all symptoms she was discharged from hospital.

It has been suggested that the absence of agglutinins is against the causation of dysentery by *Bact. alcalescens* in this case. We find this hard to believe in view of its presence in overwhelming numbers and the complete failure to discover any other cause in spite of repeated examinations.

The apparent clearing up of the remaining symptoms after the administration of *B. acidophilus* culture is suggestive, and might, we think, be of use in other similar cases.

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FRANZ A. HEIMANN, M.D., L.R.C.P.

REFERENCE

- Nabarro, D., and Edward, D. G. FF. (1939). *J. Path. Bact.*, **49**, 515.

A Case of Cystic Hygroma

The following case may be considered unusual enough to warrant publication.

Early in Sept., 1942, a child aged 20 months was brought to me by her mother, who had noticed a swelling in the left side of the neck, gradually becoming more apparent since birth. I found a rounded swelling above the outer half of the left clavicle, and diagnosed a lipoma. I advised leaving it alone unless it showed signs of growing or caused pain. About a year later she was brought back to me with the complaint that the swelling was growing. This was apparent on examination. The child was admitted to Harrow and Wealdstone Hospital, and on Sept. 25, 1943, under general anaesthesia, a large cystic tumour was dissected out apparently complete.