concurrent sarcoidosis, miliary tuberculosis, pneumonia, prostatectomy plus infection, prostatectomy alone, and a cerebrovascular incident, while in the remaining three patients no accompaniment was assigned. Nevertheless, two of the last three cases had, like the penultimate case cited, well-defined arteriosclerosis, as had the patient with pneumonia and the two who had just undergone prostatectomy. By contrast, in the nine females the simultaneous features were the antepartum phase in four, post-partum haemorrhage in two, the puerperium without mention of haemorrhage in one, and one had no specified concomitant.

3. *High Fatality Rate.*—Death occurred in 14 out of 18 cases, and was characterized by its rapid occurrence (three months or less in 10 cases) and by a terminal hypoglycaemia in at least nine patients, of whom two had received a timely and liberal intravenous infusion of dextrose. The four later deaths occurred two to four years later and all had signs of hypopituitarism.

4. *Lack of Clearly Specific Clinical Features.*—Remarks will be confined to the more fulminating type. Here the classical signs of hypopituitarism are absent. The hypopituitary coma was usually hypoglycaemic. Disturbed consciousness ranged from a "semi-stupor" (Kotte and Vonderahe, 1940) to profound coma (Alexander, 1953). Hypotension was at times postural (Feldman *et al.*, 1947; Poulsen, 1953).

The recognition of the Houssay change is important (Gordan, 1951), as doses of insulin otherwise safe may be fatal. The insulin-sensitivity test (Fraser and Smith, 1941) may lead to prolonged and dangerous hypoglycaemia. Moreover, even spontaneous hypoglycaemia may be severe, as in Alexander's patient, who had blood-sugar levels as low as 8 and 11 mg. per 100 ml.

Treatment must be energetic to prevent and correct hypoglycaemia and, ideally, the other deficiency features of hypopituitarism. The importance of the use of corticotrophin, cortisone, or an analogue (Sheehan and Summers, 1954) and cautious insulin therapy is absolute, while the judicious use of antibiotics for concurrent infection is assumed.

Summary

A case report and a review of the Houssay syndrome are presented. Our patient lapsed into a stupor twelve hours after an uneventful prostatectomy. This stupor continued until his death two weeks later, while from the seventh post-operative day insulin therapy was unnecessary. Hypoglycaemia was not detected, perhaps because of the dextrose-therapy. Necropsy showed a subtotal anterior pituitary necrosis, which was considered to be the cause of the amelioration of the diabetes. Histological study indicated that the onset of the anterior pituitary necrosis had occurred about one to two weeks pre-operatively, and was thus initially of the silent type. In this and many recorded cases arteriosclerosis may have predisposed to the anterior pituitary necrosis which, in our patient, may have undergone extension as a result of the anaemia and hypotension at or just after the operation. The diagnostic and therapeutic hazards of insulin are stressed. Cortisone or its equivalent is indicated. The desirability of its use in our patient was at first inapparent and later was offset by many complications.

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AN OBJECTIVE COMPARISON OF TWO RECENT NEUTRAL THEOPHYLLINE COMPOUNDS WITH AMINOPHYLLINE

BY

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Theophylline with ethylene diamine (aminophylline) is accepted as a preparation of great value in the treatment of cardio-respiratory disease. This mixture is, however, highly alkaline and irritant, causing severe pain when injected other than intravenously. Gastric disturbance is common with oral treatment, and much of the theophylline is precipitated by the acid gastric juice. These disadvantages of aminophylline have led to a search for a neutral theophylline compound suitable for oral or intramuscular administration.

Maney *et al.* (1946) prepared the soluble compound dihydroxypropyl theophylline ("neutrephylline"):

This substance is neutral in reaction and no precipitate occurs with gastric juice. Experimentally neutrephylline was shown to be less toxic than aminophylline, with comparable diuretic and vasodilator action. Less increase was produced in the force of cardiac contraction and there was no central stimulation of respiration. Colombi and Maggi (1949) report one asthmatic patient in whom a neutrephylline aerosol produced marked subjective relief with improvement of vital capacity; an aminophylline aerosol had been ineffective, probably because of precipitation in the presence of atmospheric carbon dioxide. In all other reports of treatment of cardio-respiratory disease with neutrephylline, benefit obtained could well be attributed to the simultaneous administration of digitalis and diuretics.

Baisse (1949) prepared a compound of theophylline-ethanoic acid with diethylenediamine ("etophylate"):

This also is soluble and neutral. In experimental animals the force of cardiac contraction is increased,

respiration is stimulated, and diuresis occurs (Lian and Charlier, 1951). During aerosol treatment over 10-15 days, 100 patients with dyspnoea of varying origins showed clinical improvement with increases in vital capacity of 100-200 c.cm. in most cases (Maulini and Barraud, 1952).

Other clinical trials of these theophylline preparations in respiratory disease have been subjective. Objective assessment has been confined to the effects of aerosol administration, and in many cases clinical improvement and increase in vital capacity could well be attributed to other factors. The compounds are widely used, and there appears to be great need for an objective appraisal of their value.

Method

The effects of these two theophylline compounds have been compared with aminophylline in patients with chronic bronchitis or asthma. Pulmonary function was assessed by measurement of the expiratory flow rate over the first 0.75 second of expiration as described by Kennedy (1953). This measure is an index of the maximum ventilatory capacity at a theoretical respiratory rate of 40 breaths a minute (hence E.F.R.⁴⁰). Each E.F.R.⁴⁰ value is the mean of the rates of six separate expirations. All drugs were given by intravenous injection, the doses used being 0.25 g. of aminophylline, 0.3 g. of neuphraylline, and 0.5 g. of etophylate. Ten patients received aminophylline and neuphraylline on two successive days, five receiving the aminophylline first and the other five the neuphraylline first. The mean of baseline readings recorded before the aminophylline (12.6 l./min., S.D. = 4.9) did not differ significantly from the mean before neuphraylline (12.6 l./min., S.D. = 4.1). Similarly, 10 other patients took part in the comparison between aminophylline and etophylate. The difference between the mean initial readings before aminophylline (14.4 l./min., S.D. = 3.4) and before etophylate (16.2 l./min., S.D. = 6.4) was not of statistical significance (standard error of difference = 1.4). Following the injections, the E.F.R.⁴⁰ was recorded at 5-minute, 10-minute, and 15-minute intervals.

Results

Comparison of Aminophylline and Neuphraylline.—Mean readings for the two drugs are shown in Table I, expressed as percentages of the initial reading before injection. It

TABLE I.—Mean E.F.R.⁴⁰ Values After Injection

	5 Minutes	10 Minutes	15 Minutes
Aminophylline	109.2% 94.5%	111.8% 91.5%	110.1% 91.5%
Neuphraylline			

will be seen that aminophylline produced consistent increase in E.F.R.⁴⁰, while the mean values following neuphraylline were less than the initial reading. The highest figures obtained by each patient have been separately calculated, and are shown in Table II, again expressed as percentages of

TABLE II.—Mean of Highest E.F.R.⁴⁰ Values Obtained After Injection

Aminophylline	116.5% (S.D. = 15.7)
Neuphraylline	97.2% (S.D. = 7.4)

the initial reading. The difference between these mean readings is of definite significance (standard error of difference = 5.5; 0.05 > P > 0.01). Tingling of the face and tongue, flushing, sweating, faintness, and hyperpnoea were frequent symptoms following an aminophylline injection, while neuphraylline produced no such sensation.

Comparison of Aminophylline with Etophylate.—Mean readings following these two injections are set out in Table III, again expressed as percentages of the initial readings. As before, a consistent increase followed aminophylline, while etophylate produced no such increase. The highest figures obtained by each patient after injection are

TABLE III.—Mean E.F.R.⁴⁰ Values After Injection

	5 Minutes	10 Minutes	15 Minutes
Aminophylline	110.4% 97.5%	113.4% 94.4%	112.6% 96.8%
Etophylate			

TABLE IV.—Mean of Highest E.F.R.⁴⁰ Values Obtained After Injection

Aminophylline	117% (S.D. = 8.7)
Etophylate	103% (S.D. = 6.9)

shown in Table IV. The difference is significant (standard error of difference = 3.5; 0.01 > P > 0.001). The injection of etophylate usually produced transient hyperpnoea of shorter duration than with aminophylline. A few patients noticed slight faintness with flushing of the face.

Conclusions

Neuphraylline and etophylate have been found to produce no increase in the expiratory flow rate of patients with chronic bronchitis and asthma, while this measurement shows improvement following aminophylline.

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COMBINATION OF CHLORPROMAZINE, PROMETHAZINE, AND PETHIDINE IN TREATMENT OF ECLAMPSIA

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The main objective of all types of management of late pre-eclamptic toxæmia of pregnancy is to reduce, primarily, the maternal mortality and, secondarily, the foetal mortality. As the pathogenesis and aetiology of this disease have not yet been established, its management is still based on three time-honoured principles: prophylaxis, treatment of symptoms, and termination of the pregnancy.

However, once convulsions and/or coma set in, the woman is immediately in imminent danger of death because of grave disturbances of the central nervous system and other visceral conditions. The case becomes an urgent medical emergency, and treatment should be directed at once to the proper management of the grave medical symptoms without regard to the pregnancy. These disturbances in eclampsia manifest themselves in anoxia of the mother through convulsive spasms of the pharynx; in pulmonary oedema through impediment in venous return to the failing and decompensated heart, which is working under the strain of sudden and excessively high systolic and diastolic pressures; and sometimes in cerebral haemorrhage as a terminal stage of extreme hypertension. Added to these disturbances are impairment of liver function due to the toxæmia and anoxia, and of kidney function due to angiospasm and inadequate oxygenation.