in the milk-borne outbreak the ready co-operation of the general practitioners in notifying the cases made it possible to find and eliminate the source of infection with the minimum delay. Even so, it seems unnecessary to stress the personal annoyance and economic waste of an infection of this kind and its potential danger, especially to young children and to the old or debilitated; and, as apparently *Salm. thompson* readily leads to the convalescent carrier state, there is a real danger that this type of salmonella infection may become endemic if the sources of infection are not eliminated.

One such source is known to be frozen imported egg (Ministry of Health, 1956). In 1956 we ourselves examined 350 tins of this product and found that 5% were infected with salmonellae. Of this number, seven were found to contain *Salm. thompson*. Newell *et al.* (1955) found *Salm. thompson* in 20 out of 153 tins examined. It is true that, even although the constituents may have been contaminated, cakes which have been adequately heated are made safe for the consumer; but the presence of any contaminated commodity in a bakery must always constitute a risk too grave to be countenanced. The handling of infected material by workers who are largely ignorant of aseptic techniques must remain difficult to control; and sooner or later, through pressure of work or carelessness, regulations, however strict, will be disregarded. Contamination will then be conveyed from the raw ingredient to the finished article, and it only remains for conditions such as atmospheric temperature and humidity to combine to favour bacterial growth, and cakes and confections which are in effect lively cultures of pathogenic organisms will be distributed to the public.

The heat treatment of egg albumen crystals at present being carried out—that is, 127–130° F. (52.8–54.5° C.) for 10 days—seems to be satisfactory, but the evolution of an efficient pasteurizing process for whole-egg products, which at present presents great practical difficulties (Murdoch, 1956), seems really essential.

The main interest of the second outbreak is that the infection was milk-borne and due to a septicaemic type of *Salm. thompson* infection in a cow. *Salm. typhimurium* and *Salm. dublin* are the types of salmonella which most commonly infect cattle in this country (Taylor *et al.*, 1953). In adult cattle the acute infection usually takes the form of an enteritis with the likelihood of faecal contamination of the milk; but the disease may also become septicaemic, with actual excretion of the infecting organism in the milk. Thus two epidemics in Dundee in 1926 and 1927 were traced to cows with *Salm. dublin* septicaemia which were excreting the organism in the milk (Tulloch, 1939); and similarly, in an outbreak in County Durham involving 252 persons, *Salm. typhimurium* was isolated from the faeces and milk of a sick cow in a herd supplying tuberculin-tested milk (Norton and Armstrong, 1954); also Henderson *et al.* (1948) described an outbreak of milk-borne infection in Aberdeenshire traced to *Salm. dublin* enteritis in a bovine animal.

On the other hand, *Salm. thompson* infection of cattle is apparently rare. *Salm. dublin* was isolated from the faeces of 8.6% of 1,000 healthy cattle in Belfast, but *Salm. thompson* was isolated from only two animals (Murdoch and Gordon, 1953); and from England and Wales only two strains of *Salm. thompson* in 1955 and one to the middle of November, 1956, had come to the notice of the Veterinary Laboratory of the Ministry of Agriculture, Weybridge (personal communication). So far as we are aware, there is no record of any previous outbreak of milk-borne *Salm. thompson* infection, or of the generalized type of the disease in cattle.

The method of disposal of infected imported egg should be carefully considered. The finding of a bovine case of generalized infection, with resultant infection of a milk supply, presents, in our opinion, a warning against the possible disposal of rejected imported egg by its inclusion in the manufacture of animal feeding-stuffs.

Summary

Two outbreaks of *Salm. thompson* gastro-enteritis are described.

The infections are attributed to (1) Chinese egg albumen used in a bakery, and (2) a septicaemic type of disease in a cow producing infected milk.

Attention is drawn to this type of bovine disease as a source of milk-borne infection.

The importance of excluding bacteriologically contaminated commodities from bakeries is stressed.

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REFERENCES

- Henderson, A., Michie, E. J. M., Rae, H. J., and Smith, J. (1948). *Hlth Bull. (Edinb.)*, 6, 28.
Ministry of Health (1956). *Weekly Hansard*, 368, 173.
Murdoch, C. R. (1956). *Monthly Bull. Minist. Hlth (Lond.)*, 15, 243.
— and Gordon, W. A. M. (1953). *Ibid.*, 12, 72.
Newell, K. W., Hobbs, Betty C., and Wallace, E. J. G. (1955). *British Medical Journal*, 2, 1296.
Norton, R., and Armstrong, E. C. (1954). *Monthly Bull. Minist. Hlth (Lond.)*, 13, 90.
Public Health Laboratory Service Reports (1954). *Ibid.*, 13, 12.
— (1955). *Ibid.*, 14, 203.
Riddell, J. (1954). *Hlth Bull. (Edinb.)*, 12, 34.
Taylor, J., Lovell, R., and McCall, A. M. (1953). *Proc. roy. Soc. Med.*, 46, 445.
Tulloch, W. J. (1939). *J. Hyg. (Camb.)*, 39, 324.
Wilson, G. S., and Miles, A. A. (1955). *Topley and Wilson's Principles of Bacteriology and Immunology*, 4th ed., 2, 1800. Arnold, London.

THE HOUSSAY SYNDROME

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Houssay and Biasotti (1930, 1931) and Houssay (1936) demonstrated that hypophysectomy relieved the diabetes mellitus of depancreatized animals. The Houssay animal exhibited diminished glycosuria, negligible ketosis, increased insulin sensitivity, survival for months without insulin treatment, widely fluctuant glycaemia, and a tendency to progressive undernutrition and to hypoglycaemic episodes. The clinical counterpart due to natural disease, conveniently termed the Houssay syndrome, is apparently rare. Indeed, Balfour and Sprague (1949) found no true example in the records of a 15-year period at the Mayo Clinic. Apart from the sporadic literature prior to Houssay's observations, 17 well-documented cases (listed in the discussion) have since been recorded.

The varied clinical patterns of hypopituitary coma (Sheehan, 1955) include three standard types—namely,

a pyrexial, a hypothermic, and a hypoglycaemic variety—as well as a miscellaneous group, into which our patient appears to fit. The explanation of his “vanishing diabetes” was elusive until the final histological demonstration of substantial anterior pituitary ablation.

Case Report

A retired clergyman aged 76 was admitted to hospital on May 8, 1955, for the stabilization of his recently self-diagnosed diabetes mellitus. His only salient illness was an attack of malaria 20 years earlier. In six months he had noted an unexplained loss of weight of 14 lb. (6.4 kg.) and he then weighed 168 lb. (76.2 kg.). His remaining symptoms were loss of appetite and energy, an increase in thirst and in both frequency and hesitancy of micturition.

He was an intelligent witness, of good physique and colour. The main abnormalities were:—skeletal and tegumentary: Heberden's nodes; vascular arteriosclerosis, without loss of peripheral pulses, and a blood pressure of 155/100 mm. Hg; alimentary: hepatic enlargement to 1 cm. below the right costal margin; urological: phimosis with mild balanitis and a firm enlarged prostate. His haemoglobin was 15.3 g. per 100 ml., and leucocyte count 7,900 per c.mm. The chest x-ray film was normal, except for marked unfolding of the aorta. The blood urea was 37 mg. per 100 ml. The Wassermann reaction was negative. The initial glucose-tolerance test showed a frankly diabetic curve—that is, fasting value, 444 mg. per 100 ml.; three-quarters of an hour after 50 g. of glucose, 546 mg. per 100 ml.; two hours after glucose, 586 mg. per 100 ml. There was no ketonuria, but the “fasting urine” contained 3.9 g. of glucose per 100 ml. and the specimen taken two hours after the ingestion of glucose 6 g. per 100 ml. After stabilization, the blood-glucose values (May 26) were: fasting, 92 mg. per 100 ml.; pre-lunch, 137 mg. per 100 ml.; pre-tea, 87 mg. per 100 ml.

Progress

On the second day in hospital he had acute retention of urine. In view of his phimosis a Riches suprapubic catheter was inserted. The diabetes was stabilized on a diet of 20 black and 14 red Lawrence lines (200 g. of carbohydrate, 105 g. of protein, and 125 g. of fat) and an injection of 46 units of insulin zinc suspension daily. The “clintest” for glycosuria now showed regular green colours, and the “acetest” (modified nitroprusside test) no ketonuria.

On June 17 he underwent a prostatectomy and a circumcision. That day his dose of insulin zinc suspension was reduced from 46 to 26 units, so that complementary soluble insulin could be continued post-operatively. Instead of lunch he received 50 g. of glucose orally, three hours pre-operatively. The operation, which ensued without cardiovascular or respiratory incident, lasted one hour. The immediate post-operative blood-sugar level was 87 mg. per 100 ml. On regaining consciousness about one hour after the operation he was given 50 g. of glucose orally. This dose was repeated four hours later. We tried throughout to avoid hypoglycaemia because of its danger in the presence of arteriosclerosis. Strict attention was given to glucose administration and to the use of a modified scale of dosage of soluble insulin, according to the results of four-hourly clintests—that is, when red or orange, 20 units; when yellow, 10 units; and otherwise, no insulin. Histologically, the prostate showed benign hypertrophy.

June 18.—In the early hours of the first post-operative day it was observed that he could not be fully roused. The cardiac rate was 96 a minute, the rhythm was regular, and the blood pressure was 100/75. Although he was not perspiring, hypoglycaemia was considered. However, 70 g. of glucose intravenously had no alerting effect. His blood-glucose level was determined on a specimen taken two hours later. The value was 462 mg. per 100 ml. He remained stuporous, mute, and rather inert, but obeyed simple commands. No abnormal neurological signs were elicited. The temperature was normal. There was no clinical or urinary

evidence of ketosis. As his confusional state persisted, a test dose of 10 mg. of amphetamine sulphate was given intramuscularly. It had no rousing effect. It was found that his haemoglobin level had fallen to 11.1 g. per 100 ml., so 2 pints (1,140 ml.) of blood was transfused. Although he swallowed small feeds of milk and fruit juice a dextrose-saline infusion was continued after the transfusion, using normal saline with the first pint (570 ml.) of dextrose and, thereafter, N/5-strength saline.

June 19.—Stupor persisted. His blood-sugar level was 190 mg. per 100 ml. The blood pressure was 110/80.

June 20.—In the morning there was no clinical change. By now the clintest usually showed green, and a daily dose of 10 units of soluble insulin sufficed (see Table). In the

Daily Blood-sugar Levels and Dose of Insulin Post-operatively. Insulin was not Required after One Week

Date	Blood Sugar, 10 a.m. Values (mg./100 ml.)	Insulin (Units)
June 17. Operation	—	26 I.Z.S. 20 soluble
“ 18	358	30 soluble
“ 19	190	30
“ 20	239	10
“ 21	350	10
“ 22	320	10
“ 23	227	10
“ 24	263	10
“ 25	254	—
“ 26	185	—
“ 27	137	—

afternoon neurological signs appeared. Responses to stimuli included groaning and grimacing. He had ocular conjugate deviation to the left. The right arm was flaccid, with areflexia, but nuchal rigidity, facial paresis, grasp-reflex, and Hoffmann's and Babinski's signs were all absent. Lumbar puncture revealed normal spinal-fluid pressure. Apart from a raised glucose level (exact value undetermined), the spinal fluid was normal. The blood-urea level was 83 mg. per 100 ml. A diagnosis of cerebral thrombosis in the left hemisphere was entertained. Oral feeding with milk and solutions of vitamins was continued with the dextrose-saline infusion.

June 21.—Ocular conjugate deviation had gone. The arms were seen to move with equal facility.

June 22 and 23.—No change was detected.

June 24.—At 6.30 p.m. perspiration began. The clintest at 4 p.m. and 6 p.m. had shown a blue colour. He remained stuporous. The temperature had risen to 101° F. (38.3° C.). The haemoglobin level was 9.8 g. per 100 ml., with a leucocytosis (13,800 per c.mm.; 93% polymorphs). The pyrexia and sweating were attributed to a pyaemia from a localized cellulitis of the anterior abdominal wall. In case, however, of hypoglycaemia, 50 g. of glucose was promptly given intravenously. There was no clinical response. The 6.30 p.m. blood-sugar level was now known to have been satisfactory (102 mg. per 100 ml.). The blood urea was 131 mg. per 100 ml. The dextrose-saline drip was stopped. Further glucose was given orally, using intubation when necessary. A five-day course of oxytetracycline, 100 mg. twice daily intramuscularly, was begun.

June 25 to July 2.—Steady deterioration ensued. There were spikes of temperature to about 103° F. (39.4° C.). Oedema increased. He died quietly in the early hours of July 2. Unfortunately the blood-sugar level was not determined after June 27.

During the post-operative phase frequent blood-sugar determinations were made. All values exceeded hypoglycaemic levels. For a convenient daily comparison, the 10 a.m. values alone are set out (see Table). It is noteworthy that, after the first week of stupor, insulin was unnecessary.

Necropsy Findings

Owing to a week-end delay the necropsy was performed 48 hours after death, with, however, intervening refrigeration.

External examination showed moderate oedema of the legs and cellulitis close to the suprapubic site of cystostomy. The lungs were pale, emphysematous, and oedematous. The heart showed moderate sclerosis of the coronary arteries, which were patent. The pancreas contained an unsuspected carcinoma of the tail, with axial spread to the body of the organ. Some small metastases of this tumour were present in the liver, and also tiny infarcts and abscesses. There were a few septic infarcts in the spleen and kidneys. The bladder showed haemorrhagic cystitis. The brain and the pituitary gland were macroscopically normal.

The significant histological findings were: adenocarcinoma of the pancreas, with destruction of islet cells; extensive anterior pituitary necrosis (Figs. 1 and 2);

FIG. 1.—Pituitary gland section, passing through upper part of gland at genu of stalk into posterior lobe. Some 10 to 20% of gland has survived (black) at this level, where survival of anterior lobe is best in all instances of pituitary necrosis. In terms of total gland volume, however, about 95% has suffered necrosis. ($\times 6$.)

secondary carcinoma and numerous areas of necrosis in the liver (where the polymorph reaction around the necrotic areas was partly due to the necrosis and partly to the infection, but the "primary" condition was the necrosis, which was probably caused by tumour growth obstructing the vessels); hepatic necrosis of about one week's duration unrelated to the pituitary necrosis; and, finally, inflammation of the glomeruli in the kidneys.

The pituitary histology merits special consideration. The age of the lesion was judged to be about three to four weeks, based on evidence from cases of post-partum necrosis where the exact time of onset and the time of survival of the patient are known.

FIG. 2.—Pituitary gland as seen under high-power microscopy. Normal parenchyma (black) is seen in right-hand lower corner and advanced necrosis in the diagonally opposite corner, with an intervening broad band of repair. ($\times 60$.)

The central parts of the necrotic areas displayed the usual total loss of nuclei; the margins of the necrotic zone showed re-opening of sinuses, complete removal of necrotic debris, loose fibrous tissue or condensed stroma, and a general appearance of good healing; the remaining parenchyma was sharply outlined, and contained the three basic types of cells.

Comment

Certain aspects of our case warrant elucidation.

1. The stupor was of an unusual and ill-defined type, remotely akin to akinetic mutism (Cairns, 1953), except that limb movements were occasionally observed. Primarily, it conformed neither to the types with striking thermal changes nor at all to the hypoglycaemic variety. There was no katatonia. The demeanour was placid, and neither tremors nor convulsions were detected. At least twice he seemed anxious to speak, but was unsuccessful. Unlike the case of Feldman *et al.* (1947), our patient did not seem to recognize surrounding objects. Neither amphetamine nor intravenous dextrose had an alerting effect.

2. The lack of dependence on insulin therapy after the first week of stupor aroused speculation. His general deterioration precluded an improved production or utilization of insulin. The assumed evidence of a cerebral infarct prompted the suggestion of a simultaneous ischaemic necrosis of the anterior hypophysis. At necropsy, however, a careful search failed to disclose a cerebral infarct.

3. Anterior pituitary necrosis, although not apparent macroscopically, was gross microscopically—a reminder that pituitary histology should not be glibly overlooked.

4. The estimated duration, histologically, of the pituitary necrosis was certainly over a fortnight but less than six weeks before death. This estimation denotes a pre-operative onset of a silent type. There was no complaint of severe headache such as Harvey and de Klerk (1955) have stressed.

5. The cause of the pituitary necrosis invites comment. His undoubted arteriosclerosis may have predisposed. This view is supported by a wider analysis of the case. It may be significant that six of the nine male patients discussed below had well-marked arteriosclerosis. Perhaps in some of the inexplicable cases a silent anterior pituitary infarct, analogous to the concept of silent myocardial infarct, had ensued. Our patient showed no distress during the operation, but the accompanying anaemia and hypotension might have facilitated the extension of this lesion. The seeming paradox of the apparent absence of hypoglycaemia yet extensive anterior pituitary necrosis may be partly reconciled with the corrective dextrose therapy. The total daily carbohydrate intake was, however, not great—that is, about 200 g. during the first week of stupor and about 150 g. thereafter.

6. Appropriate therapy was hard to envisage. The later progressive toxæmia despite oxytetracycline medication, mounting azotaemia, water retention, and a presumed cerebrovascular lesion all militated against the use of cortisone, which was earlier withheld because of a seemingly inadequate rationale. Indeed, we then argued that such treatment would only aggravate the diabetes.

Discussion

The Houssay syndrome due to natural disease, excluding acromegaly and parapituitary tumours, has been reported in 17 well-documented instances (Kotte and Vonderahe, 1940; Feldman *et al.*, 1947; Vanderbroeck and Félin, 1947; Marzullo and Handelsman, 1951; Williams, 1952; Israel and Conston, 1952; Poulsen, 1953; Alexander, 1953; Martin and Pond, 1954; Levin, 1954; Rothfeld and Rodas, 1954; Brenner, 1955; Brouwer and Schopman, 1955; Harvey and de Klerk, 1955, three cases, of which Case 2 is identifiable with fuller detail in Harvey and Bordley's book (1955); Brennan *et al.*, 1956, Case 3).

Analysis, including our patient, clearly reveals:

1. *Heterogeneity of Group.*—Age and duration and severity of the antecedent diabetes have varied widely (Harvey and de Klerk, 1955). There is no evident sex predilection.

2. *Frequently Ill-explained Hypopituitarism.*—The Houssay change often synchronized with apparently irrelevant and diverse conditions. For instance, in the subgroup of nine male patients, individual mention was made of

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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REFERENCES

- Alexander, R. I. (1953). *British Medical Journal*, 1, 1416.
 Balfour, W. M., and Sprague, R. G. (1949). *Amer. J. Med.*, 7, 596.
 Brennan, C. F., Malone, R. G. S., and Weaver, J. A. (1956). *Lancet*, 2, 12.
 Brenner, J. H. (1955). *Diabetes*, 4, 223.
 Brouwer, K., and Schopman, W. (1955). *Ned. T. Geneesk.*, 99, 1506.
 Cairns, H. (1953). *Brain*, 75, 109.
 Feldman, F., Roberts, J. B., Susseiman, S., and Lipetz, B. (1947). *Arch. intern. Med.*, 79, 322.
 Fraser, R., and Smith, P. H. (1941). *Quart. J. Med.*, 10, 297.
 Gordan, G. S. (1951). *Year Book of Endocrinology*, p. 24. Year Book Publishers, Chicago.
 Harvey, A. McG., and Bordley, J. (1955). *Differential Diagnosis: The Interpretation of Clinical Evidence*, p. 532. Saunders, Philadelphia.
 Harvey, J. C., and de Klerk, J. (1955). *Amer. J. Med.*, 19, 327.
 Houssay, B. A. (1936). *New Engl. J. Med.*, 214, 971.
 — and Biasotti, A. (1930). *Rev. Soc. argent. Biol.*, 6, 251.
 — (1931). *Pflügers Arch. ges. Physiol.*, 227, 664.
 Israel, S. L., and Conston, A. S. (1952). *J. Amer. med. Ass.*, 148, 189.
 Kotte, J. H., and Vonderahe, A. R. (1940). *J. Amer. med. Ass.*, 114, 950.
 Levin, M. E. (1954). *Ann. intern. Med.*, 40, 1230.
 Martin, M. M., and Pond, M. H. (1954). *Ibid.*, 14, 1046.
 Marzullo, E. R., and Handelsman, M. B. (1951). *Ibid.*, 11, 537.
 Poulsen, J. E. (1953). *Diabetes*, 2, 7.
 Rothfeld, B., and Rodas, J. M. (1954). *Ann. intern. Med.*, 41, 140.
 Sheehan, H. L. (1955). *British Medical Journal*, 2, 1022.
 — and Summers, V. K. (1954). *Ibid.*, 1, 723.
 Vandenberg, J., and Féry, J. (1947). *Ann. Endocr. (Paris)*, 8, 366.
 Williams, F. W. (1952). *Diabetes*, 1, 37.

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,