no evidence that common disorders of the gastro-intestinal tract produce furring in the way diseases of the mouth, throat, or lungs produce furring.

Similarly, in orthopaedic diseases, neuroses, eye diseases, and skin diseases furring of the tongue occurred no more commonly than in the control group (Table VI), and in fact the proportions of clean, intermediate, and furred tongues are surprisingly constant in all these groups of diseases. The cases of furred tongue that do occur are mostly to be attributed to smoking.

Discussion

These results show that furring of the tongue is most common in infections of the respiratory tract, in fever, regardless of the cause, in local infections of the mouth, and in heavy smokers; there is no evidence that disease of the gastro-intestinal tract produces furring unless the disease happens also to cause a fever. In particular, there is no evidence of any connexion between constipation and a furred tongue. In the common non-infective conditions of general practice, such as orthopaedic diseases, neuroses, eye diseases, and skin diseases, there is likewise no evidence of any connexion with furring of the tongue.

The division between conditions causing furring and those not causing furring is not, however, hard and fast, for one comes across cases in the former group with clean tongues, and cases in the latter group with unexplained furring, and it may be that some people always have furred tongues, even though perfectly healthy.

Nevertheless, in most cases of furring of the tongue the cause of the furring is probably to be found in one of three conditions: local infection, a dry mouth, or the irritant effect of tobacco smoke. Local infection may come from the mouth itself (as in stomatitis), or from the nose or throat (as in tonsillitis, colds, and sinusitis), or from the lungs (as in bronchitis and pneumonia). Dehydration of the mouth may result from a general state of dehydration, or from the dry mouth of a fever, or from blocked nose, and smoking presumably acts by the direct irritant action of tobacco smoke on the tongue.

This means that furring of the tongue is produced by some local change from normal conditions, and not by a change in the condition of the stomach, large bowel, or any other internal organ. Thus the value of a furred tongue as a clinical sign is distinctly limited. Furring of the tongue is commonly mentioned, for instance, as a sign of some importance in the diagnosis of acute appendicitis, and during this investigation two patients were seen with acute appendicitis, and both of them had furred tongues, but both had fevers. I suspect that the common finding of a furred tongue in acute appendicitis is due to the fever rather than to the site of the infection, and in other diseases causing abdominal pain and a fever (such as urinary infections, mesenteric adenitis, or gastro-enteritis) a furred tongue is to be expected because of the common factor of the fever and therefore cannot be relied on as indicating the site of the disease.

So far as I am aware, the only similar survey of furred tongues is that undertaken by Gans (1954). He examined the tongues of 750 children and came to the conclusion that a furred tongue is of no significance. His results, which at first sight seem to be at variance with the results quoted here, are probably due to the fact that he was seeing the children at an out-patient clinic at a hospital. Since children do not (generally) smoke, most cases of furred tongues in children occur during the course of an acute infection, typically acute tonsillitis or one of the infectious fevers, or stomatitis, and it is unlikely that many of the children that attended Gans's clinic were suffering from an acute infection. Even those children with a history of a recent infection of the respiratory tract would not be expected to show an increased incidence of furring, for the fur on the tongue disappears soon after the temperature comes down to normal. There is, in fact, agreement between these conclusions and those of Gans's in that they emphasize the unreliability of a

furred tongue as a clinical sign in the chronic and non-infective diseases. In particular, we agree that there is no connexion between constipation and a furred tongue.

Summary

An investigation into the causes of a furred tongue has been undertaken.

Seven hundred patients who were seen in general practice provided the material for the investigation.

A furred tongue is usually due to smoking, to an infection of the respiratory tract, to a fever (regardless of the cause), or to an infection of the mouth.

Furring of the tongue is not connected with disease or disorder of the gastro-intestinal tract as such.

I wish to thank Dr. S. C. Truelove, of the Radcliffe Infirmary, Oxford, for his help in designing the investigation and in writing this paper.

REFERENCE

Gans, B. (1954). *British Medical Journal*, 2, 1146.

THYROTOXIC COMA (APATHETIC CRISIS)

BY

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Symptoms of irritability, restlessness, and mental instability occur in most cases of thyrotoxicosis, and in the late stages of the disease these disturbances may acquire a more serious character. A thyroid crisis may present as an acute delirium. In contradistinction to delirium, another form of disturbance has been described—thyrotoxic coma (Lahey, 1928; Crotti, 1938; Zondek, 1944). In this paper we describe the treatment of two such cases of coma in thyrotoxic patients recently admitted to the Royal Victoria Hospital. One case terminated fatally—as has been usual in this condition—the second patient recovered, after three days in coma, following intravenous therapy with adrenocortical extracts and chlorpromazine ("largactil").

Case 1

A male cleaner in a transport department, aged 53, was admitted to hospital on July 21, 1954, complaining of a loss of 2 st. (12.7 kg.) in weight during the previous twelve months. He stated that his pulse had become fast and that there had been a great increase in the degree of sweating. Despite the weight loss his appetite had increased and he "was always hungry." Several years previously he had noted the development of a goitre, which had got progressively larger and was now accompanied by some difficulty in swallowing and huskiness of the voice. During the week before admission he had become very "nervous" and irritable, with impairment of memory and concentration. Elucidation of the history was difficult, as he was very talkative, but his cerebration was slow and his memory for dates of the onset of the complaints poor.

On examination there was evidence of weight loss and the skin surfaces were moist, particularly in the axillae. The thyroid gland was uniformly enlarged and of normal consistency, and a systolic thrill and bruit were present. The palms were warm and moist, with a fine tremor of the outstretched hands. The body temperature was 98.2° F. (36.8° C.). The pulse rate was 110, of high volume and tension, with a collapsing quality. The blood pressure was 170/80. A soft grade II precordial systolic murmur was present. No abnormalities were detected in the respiratory and alimentary systems. Exophthalmos and lid-lag were present.

Special Investigations.—The B.M.R. was +86%. The serum cholesterol was 309 mg./100 ml.; haemoglobin, 13 g./100 ml.; Haldane (88%); erythrocytes, 4,330,000 per c.mm.; M.C.V., 92 cubic microns; M.C.H.C., 33%; white cells, 3,600 per c.mm.; E.S.R., 4 mm. in one hour. X-ray examination of the thoracic inlet showed that the trachea was not deviated in either plane, but there was distinct narrowing in the region of D 1 and 2, with considerable shadowing of the soft tissue in front of and behind the trachea at this level and above.

Methylthiouracil, 200 mg. three times a day, was started. On the fourth day of treatment the patient became more disorientated and irrational. On the eighth day his evening temperature was 100° F. (37.8° C.) and the pulse 110, but no obvious infective cause was found on physical examination. On the ninth evening his temperature was 101° F. (38.3° C.), and at this stage he lapsed into coma. The white-cell count was 6,950 per c.mm. The cerebrospinal fluid contained 4 cells per c.mm.; protein, 60 mg./100 ml., a trace of globulin; the Wassermann reaction was negative; and the fluid was sterile after 48 hours' culture. Penicillin, 1 mega unit intramuscularly every three hours, was given. During the night his temperature continued at the same level. The next morning he was still comatose, perspiring excessively, and evidently becoming dehydrated, so intravenous fluid therapy was instituted. Attempts were made to lower the temperature by hourly sponging, and chlorpromazine, 50 mg. intramuscularly, was given three times a day. His temperature fell to 100° F. (37.8° C.), but it was found that he had now developed anuria. Serum electrolyte results in mEq/l., and in g./100 ml. in parentheses, were: sodium, 167 (385); chloride, 112 (655); potassium, 4.4 (17.1); CO₂-combining power, 21 (47 vols.%); blood urea, 155 mg./100 ml.

A stomach tube was passed and the diet devised by Bull *et al.* (1949) was given by this means. The patient's coma gradually became lighter over the next 36 hours, the temperature being controlled by intramuscular chlorpromazine. At this stage a fulminant diarrhoea developed; this could have been due either to the type of peanut oil used in the diet, for apparently this is an occasional hazard of this regime, or to the thyrotoxicosis. The patient died within twelve hours of the onset of the diarrhoea. Permission for a post-mortem examination was refused.

Case 2

A painter aged 39 was admitted to hospital in a comatose condition on October 11, 1954. His wife said that he had suffered from a goitre for some years but had not worried about it. Recently he had become increasingly irritable and nervous, with progressive weight loss and increasing prominence of his eyes. On the day before admission the nervous symptoms had been very pronounced. A particular incident had occurred on that day when the patient had been unable to button his child's coat owing to a pronounced tremor. On awakening on October 11 his speech was incoherent and within the course of about two hours he lapsed into coma.

On examination the patient did not respond to painful stimuli. The axillary temperature was 103.2° F. (39.6° C.) and the pulse rate 160. Perspiration had pooled in the suprasternal notch and the skin was hot, glistening, and moist. There was a marked uniform enlargement of the

thyroid gland, and on auscultation a vascular "hum" was heard. The blood pressure was 100/60, and, apart from tachycardia, the cardiovascular system was normal. The respiration rate was 40, with normal breath sounds over both lung fields. The tongue and mucous membranes of the mouth were dry. The only other abnormal physical findings were exophthalmos and enlargement of the spleen to one fingerbreadth below the costal margin. There was no neck stiffness and the retinae showed no abnormality.

Special Investigations.—On admission the electrolyte concentrations in mEq/l., and in g./100 ml. in parentheses, were: sodium, 153 (351); chloride, 101 (590); potassium, 4.3 (16.7); CO₂-combining power, 18 (39 vols.%); serum calcium 4.7 (9.4). The blood sugar was 138 mg./100 ml. Agglutination reactions for typhoid, paratyphoid A and B, *Brucella abortus*, and *Leptospira icterohaemorrhagiae* were negative in all dilutions. The haemoglobin was 11.2 g./100 ml.; Haldane (76%); E.S.R., 7 mm. in the first hour; leucocytes, 9,400 (81% neutrophils); serum proteins, total 5.7 g./100 ml. (albumin 3.1 g., globulin, 2.6 g.); thymol turbidity, 1 unit; alkaline phosphatase, 8 units.

A provisional diagnosis of thyrotoxic coma was made and measures were started at once to reduce the body temperature and maintain a normal fluid balance. The patient was covered with a cold wet blanket and a fan was directed to play across the bed. Intravenous fluid therapy was started, and in the next 24 hours 7.5 litres (13 pints) of fluids were administered as alternate bottles of 5% glucose and normal saline. To these fluids were added a total of 30 ml. of 0.8% collosol iodine, 60 ml. of "eucortin," and 225 mg. of chlorpromazine. Intramuscular corticotrophin, 100 mg. daily, and penicillin, 2 mega units daily, were also given. Throughout this time the axillary temperature had varied between 102 and 104° F. (38.9 and 40° C.) but at 15 hours a rapid fall took place to 99° F. (37.2° C.). During this period oxygen was administered through a B.L.B. mask. In the second 24 hours a total of 4.5 litres (8 pints) of fluids was administered intravenously, containing 75 mg. of chlorpromazine. A stomach tube was passed and 2 oz. of milk with a liquid vitamin supplement was given by this means every hour.

At 52 hours his condition changed from that of a coma to restlessness, and he persistently attempted to paint the air around his bed with his right hand while "smoking" an imaginary cigarette with his left hand. From 52 hours to about 80 hours he became more restless and noisy. He talked incessantly, addressed the medical staff by various Christian names, and carried on conversation with imaginary people around his bed. He was hyperkinetic and excitable to an extreme degree—visibly starting when his bed was approached. During this stage he required large doses of paraldehyde intramuscularly. On the fifth day he relapsed into stupor and the axillary temperature rose to 102° F. (38.9° C.) but was controlled by surface cooling and 100 mg. of chlorpromazine intravenously. From the first day of treatment 800 mg. of methylthiouracil had been crushed and given by stomach tube each day.

On the third day slight icterus of the conjunctivae developed and the serum bilirubin was 1.2 mg./100 ml. The cerebrospinal fluid was clear with a free rise and fall, and contained 4 leucocytes per c.mm.; protein, 45 mg./100 ml., with a trace of globulin; the Wassermann reaction was negative. X-ray examination of the chest revealed no abnormality. Two blood cultures were sterile. An electrocardiograph showed sinus tachycardia, and the electroencephalographic report stated: "There is no alpha rhythm. There is a dominant frequency at 6.7 c/s of low amplitude and fair symmetry. No focus seen. There is excess artefact due to sweating."

Operation and Pathology.—Recovery was uneventful from the seventh day onwards, and on the 30th day after admission a subtotal thyroidectomy was carried out by Mr. E. W. Morrison, who reported: "Both lobes were enlarged to about ten times normal size; the gland was very vascular and obviously hyperactive." The pathological report

(Dr. W. T. E. McCaughey) stated: "The enlarged thyroid lobes contained several small cysts, which on microscopical examination were seen to be re-epithelizing colloid nodules. The thyroid acini appeared moderately active with increased height of the epithelium and in areas there was papillary infoldings of the acinar walls."

Discussion

The incidence of thyroid crisis as seen by Means and his co-workers over a period of 25 years was 36 out of a total of 2,033 cases of thyrotoxicosis admitted to the wards of the Massachusetts General Hospital (McArthur *et al.*, 1947). The classical picture of thyrotoxic crisis is that of a hyperpyrexia associated with delirium and irritability. As opposed to this activated crisis, Lahey (1928) has described a form in which this complication may present as extreme prostration with mental apathy passing on into coma—"apathetic" crisis. This coma type of crisis presented only twice in the above series of 36 cases of McArthur *et al.*, so that it appears to be a very rare condition indeed, occurring approximately once in a thousand thyrotoxic cases.

Description of Coma.—"Coma basedowicum" was regarded by Zondek (1944) as the most severe manifestation of thyrotoxicosis, and he has described in detail three such cases. The first was that of a married woman aged 32 who died within three days of the onset of severe symptoms. Her condition was described as "immobile and stuporous, temperature 102° F. (38.9° C.), with extreme tachycardia." The second case was that of a married woman aged 31 in whom death resulted within five days of onset with "marked pyrexia and tachycardia." Recovery occurred in the third case, but this patient was not fully comatose: "patient can hardly speak, is weak and quite confused, unable to raise her head, the jaw hangs down."

Causation

The mechanism whereby uncontrolled hyperthyroidism can cause these profound changes usually terminating in death is not known. We also do not know whether there is any difference in the pathogenesis of the classical crisis and the rarer type presenting as a coma. The concentrations of the chief electrolytes of the blood were found by Maddock *et al.* (1937) to be normal in the early stages of crisis. A decreased adrenal reserve occurs in hyperthyroidism as measured by the response to corticotrophin of eosinophils, ketosteroids, and formaldehydogenic steroids (Daughaday and Farr, 1951). It has been suggested that the initiation of a thyrotoxic crisis or its severity may depend upon an inadequate adrenocortical response to the stress imposed by severe thyrotoxicosis. Evidence of impaired liver function has been demonstrated frequently (Youmans and Warfield, 1926; Boyce and McFetridge, 1938; Ficarra and Naclerio, 1945). Crile (1940) was of the opinion that this was the most common single cause of post-operative confusion and delirium in patients with hyperthyroidism. Many other hypotheses of causation of crisis have been proposed—thyroid failure (Litchford, 1935), anaphylactoid reaction (Herget, 1940), iodine lack (Waldenström, 1945), acute hypothyroxinaemia (Mahaux, 1946).

Post-mortem studies in most cases of crisis have been of little help, and Ransom and Bayley (1934), reporting on 14 fatal cases, concluded that the conditions found, such as cardiac dilatation and bronchopneumonia, were not the primary cause of death. The findings of Foss *et al.* (1939) in their 20 cases of crisis were that there was insufficient proof to attribute the cause of death primarily to any one organ.

Uncontrolled Hypermetabolism as the Cause of Crisis.—Means (1948) regards thyrotoxic crisis or "storm" as representing a breakdown in the body's ability to withstand any longer the burden of its thyrotoxicosis. "It may be looked upon as decompensated thyrotoxicosis, the adjective being used in a way analogous to that in 'decompensated heart disease.'" If the adverse effects of prolonged hypermeta-

bolism are studied it is evident that Means's theory of decompensation explains adequately most of the observed phenomena. Increasing metabolism causes a relative tissue anoxia and difficulty in heat elimination. With the onset of pyrexia the whole process becomes accelerated: "a thyroid crisis is a vicious circle of hyperthermia and hypermetabolism, with each degree of elevation of temperature there is an increase of 7.2% in the B.M.R., and with each increase in the rate of metabolism there is proportionate increase in the production of heat by the body" (Crile, 1942).

"Decompensation" manifests itself initially as a rise in body temperature; an attempt is made to shunt more blood from the internal organs to the skin vessels in order to increase heat loss, and this leads to fluid depletion and shrinkage of the vascular volume with a resulting accentuation of the relative anoxia of the internal organs. Furthermore, the need of the internal organs for oxygen is probably greatly in excess of normal. The sensitivity of animals to lowered oxygen pressure is accentuated following the administration of thyroid powder (Kessler and Gellhorn, 1942), and the oxygen consumption *in vitro* of the excised brains of hyperthyroid animals was found to be increased as much as four times that of normal brains (Cohen and Gerard, 1937). The oxygen consumption of the splanchnic area in hyperthyroidism is increased (Myers *et al.*, 1950). Buxton (1944) was of the opinion that many of the features of crisis were the result of anoxia in the central nervous system—the milder cases having general features similar to that seen in "mountain sickness." "The symptoms of fulminating crisis are those of a severe acute oxygen deprivation—namely, delirium, hyperpyrexia, and coma." The insoluble dilemma for the severe thyrotoxic appears to be that of the opposing demands of the internal organs and the peripheral circulation on the cardiac output.

Treatment

The aim of therapy in this condition must be to prevent tissue anoxia and at the same time increase heat loss. Treatment of thyroid crisis in the past has consisted in sponge baths to combat pyrexia; parenterally administered fluids containing glucose and suitable electrolytes to correct dehydration, hepatic glycogen depletion, and electrolyte disturbances; oxygen to prevent tissue anoxia and sedation for irritability. Prophylactic chemotherapy and vitamins have been given, and adrenal cortical extract to compensate for possible adrenal cortical exhaustion (McArthur *et al.*, 1947). Treatment aimed at reducing thyroid activity has been limited by the relative slowness in action of the thiouracil derivatives.

Adrenocortical extract has been used previously on the basis that in thyrotoxic crisis there was a relative adrenal insufficiency. There is experimental and clinical evidence that adrenocortical secretion causes a depression of thyroid function and that its efficiency may be related more to this action. A diminished uptake of radioactive iodine took place in the glands of experimental animals following treatment with cortisone (Hardy *et al.*, 1950). Six cases of thyrotoxicosis have been treated with corticotrophin in doses of 40 to 200 mg. a day, and in three cases a depression of thyroid activity was observed as measured by determination of protein-bound iodine and basal metabolic rates (Hill *et al.*, 1950). Corticotrophin was also used by Szilagyi *et al.* (1952) in three cases of thyrotoxic crises that had been unresponsive to other measures, but following the administration of corticotrophin improvement took place, with recovery in all three cases. In Case 2 intravenous cortical extract and intramuscular corticotrophin were used, as it is probable that this combination causes the most rapid augmentation of circulating adrenocortical substances. (Intravenous hydrocortisone, which has recently become available, might be used in any future case.)

Chlorpromazine has been used in the production of artificial hibernation (Laborit and Huguenard, 1952) and induced hypothermia (Dundee *et al.*, 1954). These authors concluded

that the effectiveness of chlorpromazine was due to a two-fold action—a depression of shivering combined with a peripheral vasodilatation. Decourt *et al.* (1953) believe that its hypothermic properties depend almost entirely on its cellular hypometabolic action rather than on the autonomic nervous system. Ratschow (1953) found a 20% reduction in basal metabolism following chlorpromazine administration, and Bobbio *et al.* (1952) described a patient undergoing splenectomy who had a basal metabolic rate of +48% before operation, but during hibernation a fall occurred to +10%, which was maintained for about 48 hours. These workers showed also that the combination of surface cooling and hibernating agents had a depressing action on the thyroid as shown by a fall in the radio-iodine uptake of the thyroid glands of experimental animals.

There have been reports of liver damage following the use of chlorpromazine, and the risk involved in its administration during thyrotoxic crisis is that the anoxic injury to the liver may be accentuated. The liver-function tests in Case 2 showed a slight rise in the serum bilirubin concentration on the third day of the crisis, but further tests at later dates were normal.

Conclusion

Thus it seems that thyroid crisis can be explained as the result of prolonged hypermetabolism in uncontrolled thyrotoxicosis, and it should be regarded as an imminent risk in severe and inadequately controlled thyrotoxic patients.

Lahey repeatedly called attention to the importance of this condition and the necessity for adequate treatment: "Just as there is an emergency treatment for impending diabetic coma, there should be, and is, an emergency treatment for the impending thyroid crisis."

Summary

Two cases of thyrotoxic coma are described and the incidence of this complication in thyrotoxic subjects is discussed.

A survey is made of the literature dealing with the pathogenesis of thyrotoxic coma and its relationship to thyroid crisis. Uncontrolled hyperpyrexia and anoxia of the internal organs were considered to be important in the development of this complication.

Hitherto the recommended treatment has been that of fluid and electrolyte replacement with oxygen administration. It is suggested that adrenocortical extracts and chlorpromazine are useful adjuncts to this therapy.

ADDENDUM.—Since this paper was submitted for publication there has been reported the successful treatment of a case of thyroid crisis in which chlorpromazine was used as an aid to cooling (Hunter, 1955).

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DIABETES INSIPIDUS IN ASSOCIATION WITH POST-PARTUM HYPOPITUITARISM

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The great majority of cases of hypopituitarism in women are now believed to be due to post-partum necrosis of the pituitary anterior lobe. Sheehan (1939), in an important paper on the subject, has fully established post-partum hypopituitarism as a clinical entity and has fully described the rather variable clinical picture. Since then an extensive literature on the subject has accumulated. Sheehan and Summers (1949) note that serious haemorrhage or collapse at the time of delivery is nearly always the determining factor in its occurrence.

The extent of the necrosis is, in general, roughly proportional to the patient's condition at delivery. It is probable that at least 80% of the anterior lobe must be destroyed before severe symptoms are produced.

The occurrence of symptoms of diabetes insipidus in association with post-partum necrosis and anterior pituitary insufficiency is exceedingly rare and is a striking phenomenon. It was first seen by Suchier (1927). Spain and Geoghegan (1946), at necropsy, found necrosis in both the anterior and the posterior lobes of the pituitary body. Other similar cases have been reported (Nassar *et al.*, 1950; Storti and Pederzini, 1952; Bracali, 1953; Engstrom and Liebman, 1953; Destro, 1953; Bottura *et al.*, 1954; MacGillivray and Adams, 1954) in which there was disagreement with the experimental data concerning the relationship between the anterior and the posterior lobe of the hypophysis. A further case is added to the few already reported.

Case Report

A woman aged 33 who married in 1947 was in apparently good health until the birth of her child in April, 1948. She was delivered by caesarean section in the eighth month because of the occurrence of eclampsia. She had considerable post-partum haemorrhage. During the puerperium there was a complete absence of breast activity, her mammary glands became soft and involuted, and there was no secretion of colostrum or milk. Within a few days, while still in hospital, the pubic and axillary hair disappeared and the hair of her head and eyebrows became thin. Later the restoration of rhythmic ovarian function failed; menstruation did not return.

About four weeks after delivery she developed polyuria and a proportional polydipsia. The diuresis ranged between