thus appears to combine the type of growth displayed by both the pre-diabetic juvenile and the obese middle-aged diabetic.

The clinical and experimental observations discussed suggest that an excessive secretion of the anterior pituitary growth factor during pregnancy may account for the production of progressive maternal obesity, large babies, and ultimate maternal diabetes.

Summary

Twenty-one women with obstetric histories of unexplained abortions, miscarriages, intrauterine deaths, stillbirths, and neonatal deaths, and the birth of babies weighing 10 lb. or more, were admitted to hospital for investigation. Six of these patients were found to be diabetic. All six were grossly obese and five had had babies weighing 10 lb. or more.

Evidence is brought forward to show a correlation between progressive maternal obesity, the birth of unusually large babies, and ensuing maternal diabetes. It is suggested that an excessive secretion of the growth factor during pregnancy may account for the associated phenomena.

I wish to thank Professor D. M. Dunlop and Dr. R. F. Ogilvie for their helpful advice and criticism, and Professor R. J. Kellar for so kindly putting the case records of the Simpson Memorial Maternity Pavilion at my disposal.

REFERENCES

- Allen, E. (1939). *Amer. J. Obstet. Gynec.*, **38**, 982.
 Bigby, M. A. M., and Jones, F. Avery (1945). *British Medical Journal*, **1**, 360.
 Bill, A. H., and Posey, F. M. (1944). *Amer. J. Obstet. Gynec.*, **48**, 405.
 Gilbert, J. A. L., and Dunlop, D. M. (1949). *British Medical Journal*, **1**, 48.
 Henley, W. E. (1947). *N.Z. med. J.*, **46**, 386.
 Joslin, E. P. (1946). *The Treatment of Diabetes Mellitus*, 8th ed. Kimpton, London.
 Kriss, J. P., and Futcher, P. H. (1948). *J. clin. Endocrinol.*, **8**, 380.
 Lukens, F. D. W. (1946). *Amer. J. med. Sci.*, **212**, 229.
 Miller, H. C. (1945). *New Engl. J. Med.*, **233**, 376.
 — (1946). *J. Pediat.*, **29**, 455.
 — Hurwitz, D., and Kuder, K. (1944). *J. Amer. med. Ass.*, **124**, 271.
 Ogilvie, R. F. (1933). *J. Path. Bact.*, **37**, 473.
 — (1935). *Quart. J. Med.*, n.s. **4**, 345.
 — (1944). *Edinb. med. J.*, **51**, 460.
 Watts, R. M. (1935). *Amer. J. Obstet. Gynec.*, **30**, 174.
 White, P. (1946). In Joslin's *Treatment of Diabetes Mellitus*, 8th ed. London.
 — and Hunt, H. (1943). *J. clin. Endocrinol.*, **3**, 500.
 Young, F. G. (1941). *British Medical Journal*, **2**, 897.
 — (1945). *Biochem. J.*, **39**, 515.

GLOSSITIS IN ADDISONIAN PERNICIOUS ANAEMIA

EFFECT OF SYNTHETIC VITAMINS OF THE B COMPLEX

BY

ALEXANDER BROWN, M.D., F.R.F.P.S.
M.R.C.P.Ed.

(From the Muirhead Department of Medicine, the University and Royal Infirmary, Glasgow)

Glossitis has been recognized as a common feature of Addisonian pernicious anaemia since the work of Hunter (1909). Some evidence of involvement of the tongue is obtained in about 70% of cases (Brown, 1946). Adequate treatment of the anaemia with potent liver extract usually results in the disappearance of oral symptoms.

Glossitis is also a common feature of the sprue syndrome and of many deficiency states such as pellagra. Its occurrence has been attributed to deficiency of specific vitamins such as nicotinic acid and riboflavin. The fact that the sore tongue of the pernicious anaemia syndrome is indistinguishable from that occurring in well-recognized nutritional deficiencies suggests that in pernicious anaemia it may again be due to a vitamin deficiency, and that it may

be corrected by appropriate treatment with one or more of the members of the vitamin B complex.

The present report describes the occurrence of glossitis and a syndrome suggestive of ariboflavinosis in patients with Addisonian pernicious anaemia and the effect of treatment with certain synthetic vitamins of the B complex.

Clinical Observations

Seven patients with pernicious anaemia are described in whom there was a well-marked disturbance suggestive of deficiency of one or more members of the vitamin B complex. The diagnosis of pernicious anaemia was made on the following grounds. In all cases the clinical picture was compatible with the diagnosis; all had a macrocytic anaemia with a megaloblastic bone-marrow reaction which showed a satisfactory response after treatment with highly purified liver extract; all had a histamine-fast achlorhydria; and in none was there evidence of steatorrhoea or dietary defect.

Of the seven patients, six had severe painful glossitis. Five of the six had been receiving parenteral liver therapy for periods ranging from four months to two years; they were receiving it regularly every two to four weeks during the period of this present study. As indicated in the case reports, the glossitis had either existed since the original illness or developed during its treatment with parenteral liver. The development of a sore tongue was not always controlled by liver therapy, and on occasion bore no relation to the immediate or subsequent haematological status of the patient. In the seventh case (treated for five years) glossitis was associated with angular stomatitis and vascularization of the cornea.

Case 1

A man aged 58 developed pernicious anaemia, for which liver therapy was started in February, 1946. His tongue was red, glazed, and smooth, but did not cause pain until June, 1946, when its appearance deteriorated and it became extremely sensitive and painful. Blood levels at this time and during the subsequent six months were maintained above 4,500,000 red cells per c.mm. by regular administration of anahaemin. From June 15, 200 mg. of nicotinic acid daily for seven days left the condition of the tongue, if anything, worse. On June 22 100 mg. of calcium pantothenate was given intramuscularly and then 100 mg. daily by mouth.

By the third day discomfort had disappeared; by the seventh day only slight redness at the tip remained, and by July 6 the organ was merely clean and atrophic. Calcium pantothenate was stopped on July 6, and from this date only routine liver therapy was given. Lingual discomfort returned within 14 days. By July 27 the organ was diffusely red and raw-looking, painful, and extremely sensitive, with numerous deep fissures. From July 27, 100 mg. of calcium pantothenate was given daily by mouth. By the fourth day undue discomfort could not be provoked even by hot foods or by deliberate friction against the teeth. By the seventh day objective evidence had almost entirely disappeared. By Aug. 17 the tongue looked more nearly normal than at any time since the patient had first been seen. Atrophy was less marked and central furring had developed. Fissuring was no longer present. Treatment with pantothenate was discontinued, and by March, 1947, there had been no recurrence of the glossitis.

Case 2

A married woman aged 40 had received liver therapy for two years, when the tongue, previously pale and atrophic, became red and very uncomfortable. When seen with this complaint in February, 1946, blood values had been maintained for two years at normal levels (between 4,800,000 and 5,570,000 red cells per c.mm.). From Feb. 23, in addition to the continued regular administration of highly refined liver extract (anahaemin), 300 mg. of nicotinic acid was given daily by

mouth. Gradual improvement occurred, and by April 13 the only visible abnormality was slight marginal redness. The organ was still uncomfortable and unduly sensitive to hot foods. Continued treatment failed to improve matters, and nicotinic acid was stopped on April 27. She continued to receive regular injections of liver extract (anahaemin), but symptoms gradually returned. By Aug. 24 severe general glossitis was present. From this date she was given 100 mg. of calcium pantothenate daily by mouth. From the fourth day the tongue was comfortable, and by the seventh nothing abnormal was evident except slight atrophy. Treatment was stopped. Symptoms returned at beginning of November, and by the 23rd severe marginal glossitis was present, causing great discomfort. From this date she was given 100 mg. of calcium pantothenate daily by mouth. By the third day the tongue was almost completely asymptomatic. By the seventh day it looked almost normal, and by the 14th day it showed only a smooth atrophic veal-like condition. Treatment was stopped. Up to February, 1947, there had been no return of symptoms.

Case 3

A man aged 61 had received liver therapy for pernicious anaemia for nine months. His tongue had been normal in appearance and sensitivity during this period. In spite of continued regular treatment, and in the presence of blood values unchanged above 4,300,000 red cells per c.mm., from June, 1946, he gradually developed a painful glossitis. By July 27 the organ was diffusely affected and extremely sensitive and remained so without change until, from Aug. 24, 100 mg. of calcium pantothenate was given daily by mouth. Great subjective improvement was noted within 48 hours, and by the seventh day the organ was not even unduly sensitive. It was also normal in appearance. Calcium pantothenate was stopped, and up to March 15, 1947, there had been no return of symptoms.

Case 4

A married woman aged 58 had had a sore tongue before liver therapy was begun for pernicious anaemia in 1946, and during maintenance treatment which kept blood levels at above 4,500,000 red cells per c.mm. she suffered almost continuously. On June 7, 1946, after about two years' observation and treatment, the tongue showed a severe marginal glossitis with numerous sharp-edged fissures. It was extremely sensitive. By Aug. 3, in spite of continued treatment with liver extract, conditions remained unchanged. She was given 100 mg. of calcium pantothenate intramuscularly. Within 48 hours all discomfort had disappeared and within seven days signs had almost completely disappeared. Routine liver therapy thereafter failed to maintain this improvement, although the red cell count did not fall below 4,400,000 per c.mm.; but within five weeks of giving pantothenate the tongue had returned to its previous condition. On Oct. 6 a further 100 mg. of calcium pantothenate was given intramuscularly. Within 48 hours marked improvement had occurred, and by the seventh day all evidence of active glossitis had disappeared. Return of symptoms was evident in about three weeks, and by Nov. 2 active glossitis was again fully established. From this date 50 mg. of calcium pantothenate was given daily by mouth. By the third day the tongue was much less sensitive, and by the seventh day all discomfort had disappeared and the organ looked merely pale and atrophic. Treatment was stopped and conditions in the mouth remained unchanged for almost a year. In October, 1947, active glossitis again appeared, uninfluenced by continued regular administration of liver extract and with blood levels above 4,500,000 per c.mm. throughout. By Nov. 10 the tongue showed diffuse redness and was extremely sensitive. A simple dose of 50 mg. of pantothenate was given intramuscularly. Within 48 hours symptomatic relief was evident, and on the seventh day all redness had disappeared, but the tongue was atrophic. There had been no return of symptoms up to May, 1948.

Case 5

A woman aged 73 was admitted to hospital in April, 1944, on account of pernicious anaemia associated with severe glossitis and stomatitis. The tongue was diffusely red and

showed slight fissuring. The oral features were unaffected by liver therapy even when this was given twice weekly (4 ml. of anahaemin on each occasion). The blood count rose with a reticulocyte response in an unusually slow fashion, and throughout the following observation period the red cell levels failed to reach 4,000,000 per c.mm. Administration of 150 mg. of nicotinic acid daily by mouth from May 19, 1945, was followed by great improvement. By the seventh day the tongue was less sensitive and looked much less raw. The lips had healed completely. By the 14th day the tongue was merely atrophic and all discomfort had disappeared. Continuation of treatment for four months failed to improve the atrophy. After about two months' treatment with liver extract alone, active glossitis again became troublesome, and by February, 1946, the tongue had returned to its previous condition. On this occasion repetition of nicotinic acid treatment (150 mg. a day) was beneficial, but failed to relieve the condition completely. Treatment was stopped after three weeks, and 5 mg. of riboflavin was given daily by mouth from Feb. 28. Complete subjective and objective evidence of active glossitis disappeared within seven days. Treatment was stopped, and by June 3 symptoms had returned. On this date 100 mg. of calcium pantothenate was given intramuscularly. During the following 10 days the glossitis gradually became more severe. On Aug. 14 administration of riboflavin was again begun (5 mg. a day), with complete subjective and objective recovery by the seventh day. Further observations on this case were not possible.

Case 6

A married woman aged 58 was first seen on account of a sore tongue which had been troublesome for about two years. She was found to have pernicious anaemia. The tongue was diffusely red over the dorsum and very sensitive, although sensations of taste were impaired. From April 5, 1947, treatment with liver extract being withheld, 50 mg. of calcium pantothenate was given daily by mouth for seven days; no benefit resulted. After a further seven-day period of observation riboflavin was given in doses of 5 mg. daily for a week, again without benefit. Thereafter nicotinamide in daily doses of 200 mg. for two weeks was associated with slight aggravation of the glossitis. From May 10 folic acid was given by mouth in doses of 20 mg. a day. By the seventh day marked relief had occurred, and by the 10th day it was complete. By the 14th day the tongue was normal in appearance. A satisfactory haematological response also occurred with this treatment, and by Aug. 16 the tongue and the blood levels were normal. Folic acid was discontinued. Within four days the tongue became uncomfortable and active glossitis gradually progressed until liver therapy was begun on Aug. 23. Thereafter both anaemia and glossitis remained adequately controlled.

Case 7

This woman, aged 61, had been receiving liver therapy for five years, when she failed to receive adequate treatment and relapsed. During recovery from this relapse, with weekly administration of 4 ml. of anahaemin and with a red cell count of 3,410,000 per c.mm., she developed a very severe bilateral angular stomatitis involving the mucocutaneous junction, marginal glossitis, and vascularization of the cornea in the upper and outer quadrants, more pronounced in the left eye, where penetration of small vessels amounted to about 2 mm. There was also severe conjunctivitis. Treatment with riboflavin was begun on Dec. 28, 1946. Within a week the angular stomatitis and the conjunctivitis had improved, and by Jan. 25, 1947, the corneal change was seen to be receding. By Feb. 1 the tongue and lips were normal, and within a further 14 days the eyes also were normal. Riboflavin was discontinued after a short period. There was no return of symptoms.

Summary of Results of Treatment.—The results obtained by the administration of synthetic vitamins of the B complex to these patients are summarized in the accompanying table. No single substance was found to be effective throughout all cases, and although consistent results were obtained in the one individual with a single vitamin for periods up to 15 months (Case 4), it was also found in one

Table Summarizing Results of Treatment

Case No.	Sex	Clinical Status	Blood Level (Millions)	Lesions	Effective Treatment	Vitamins Ineffective
1	M	Treated 4 months	4.5 +	Glossitis	Pantothenate, oral + i.m.	Nicotinic acid
2	F	Treated 2 years	4.8-5.8	"	Pantothenate, oral	Nicotinic acid (partial effect)
3	M	Treated 1 year	4.3 +	"	Pantothenate, oral	—
4	F	Treated 2 years	4.4 +	"	Pantothenate, (1) i.m., (2) oral	—
5	F	Treated 1 year	3.5-4.0	Glossitis, stomatitis	Nicotinic acid, riboflavin	Nicotinic acid later inadequate
6	F	Untreated	3.4	Glossitis	Folic acid	Pantothenate, nicotinamide, riboflavin
7	F	Treated 5 years	3.41 +	Glossitis, angular stomatitis, vascularization of cornea	Riboflavin	—

instance (Case 5) that different vitamins might be effective at different times against apparently similar lesions.

Discussion

The significance of glossitis in pernicious anaemia is not understood, but it is generally recognized that if sore tongue is a feature before treatment is begun it is usually cured by liver extract. Indeed, so commonly does the glossitis respond to liver extract that it has been said that reappearance of tongue manifestations in patients under treatment is an indication of inadequate therapy (Wintrobe, 1946). This suggests some direct relation between the glossitis and the anaemia. There is, however, evidence to the contrary (Oatway and Middleton, 1932; Brown, 1946).

In the present series glossitis occurred without obvious relation to present or subsequent blood levels (see Cases 1, 2, and 4 especially). The significance of this is not clear, especially in view of the apparent rarity of such an occurrence in the experience of others (Wintrobe, 1946). It seems unlikely from what is known of the individual patients that exceptional dietary inadequacy was by itself responsible. All had good appetites and were taking apparently adequate diets. The possibility of a combination of minor defect of absorption in pernicious anaemia and a sub-optimal post-war dietary cannot be entirely discounted. The question arises whether increased dosage with liver extract would have been effective treatment for the glossitis. No definite answer can be given from these results, which are concerned with the effect of single pure substances, but it should be noted that blood counts were maintained at normal and even high levels (Case 2), and in spite of this the tongue was sore. In addition Case 5 received unusually large doses of liver extract without effect on the tongue.

It would seem possible that the development of a sore tongue in pernicious anaemia reflects a breakdown in a metabolic system similar to that responsible for the megaloblastic marrow and the neurological changes. The fact that in this series the glossitis could be controlled by the administration of synthetic vitamins suggests that the breakdown may involve the availability of the vitamin found effective. Members of the B complex exist in natural foods often in a conjugated and not immediately available form. The suggested breakdown in availability may occur at this stage in assimilation, or later in closer relationship to their final functions as parts of enzyme systems concerned with cellular metabolism. Liver extract contains a factor which in the majority of cases rectifies the defect responsible for the mucosal changes and at the same time corrects those responsible for the marrow and neural disturbances. Vitamin B₁₂, which may be identical with the anti-pernicious-anaemia principle of liver, has been found effective against the anaemia, the neurological changes, and the glossitis. Conceivably this substance may promote the utilization of certain other essential substances, some of which are well-known vitamins of the B complex.

The role of pantothenic acid in human nutrition is not yet fully understood, and the instances described here are

believed to be the first in which this substance has been found to influence symptoms in pernicious anaemia. If this effect represents restoration of an actual deficiency it is difficult to account for the latter except on the basis of a metabolic disturbance secondary to a more fundamental defect such as that already suggested. Pantothenic acid is widespread in Nature, and a deficiency conditioned in such a way seems more probable than one due simply to inadequate intake, especially in persons whose diet is not obviously abnormal.

Summary

Seven patients with Addisonian pernicious anaemia are described each of whom had a sore, red, raw-looking tongue. One also had angular stomatitis and vascularization of the cornea.

In each case it was found possible to control these changes with a single member of the vitamin B complex in pure form. Four cases of glossitis responded to calcium pantothenate, and one each to nicotinic acid and folic acid. One case responded first to nicotinic acid and later to riboflavin. The patient with glossitis, angular stomatitis, and vascularization of the cornea responded to riboflavin.

The significance of these findings is discussed, and it is suggested that the epithelial changes described reflect a breakdown in some metabolic system which may be similar to that responsible for the megaloblastic marrow and the neurological complications of pernicious anaemia.

I wish to thank Professor L. J. Davis for his advice and criticism in the investigations and in the writing of this paper.

REFERENCES

- Brown, A. (1946). *Glasg. med. J.*, 27, 313.
 Hunter, W. (1909). *The Severest Anaemias*. Macmillan, London.
 Oatway, W. H., and Middleton, W. S. (1932). *Arch. intern. Med.*, 49, 860.
 Wintrobe, M. M. (1946). *Clinical Haematology*. Kimpton, London.

UNUSUAL SYMPTOMS IN PETROL-TANK CLEANERS

BY

INDER SINGH, M.B., B.S., M.R.C.P., F.R.F.P.S.

Lieutenant-Colonel, I.A.M.C.

On Sept. 18, 1945, men from a certain labour unit were employed in cleaning a large petrol tank. It had just been drained of its contents, and to overcome the effects of undue exposure to the petrol vapour inside the tank the men were ordered to work in frequent shifts. The air inside the tank was not rendered gas-free, nor were the men given any airline masks or special clothing to wear. After the initial respiratory discomfort and irritation of the eyes the workmen became accustomed to the vapour and some of them stayed in longer.

Two men, whose cases are recorded below, went to the extreme and worked almost continuously for nearly seven hours. No adverse effects during this period prevented them from doing so. Towards the end, however, they