THE IMPORTANCE OF THE PLUMMER-VINSON SYNDROME IN THE AETIOLOGY OF CARCINOMA OF THE UPPER GASTRO-INTESTINAL TRACT

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ON May 2, 1919, at the Summer Congress of the Laryngological Section of the Royal Society of Medicine, two British laryngologists, D. R. Paterson and A. Brown-Kelly, independently read papers describing a quite specific type of dysphagia occurring usually in middle-aged women. The dysphagia, although sometimes of sudden onset, was usually of long standing and was referred to the level of the larynx. Both Paterson and Brown-Kelly remarked on the commonly associated atrophy of the mucosal lining of the upper gastrointestinal tract. The lesions observed were fissures at the angles of the mouth, atrophic glossitis, pale smooth pharyngeal mucous membrane and strictures or web-like deformities at the pharyngo-oesophageal junction.

Brown-Kelly, in his contribution, made passing mention of a history of anæmia in some of his patients. Two years later Porter P. Vinson (1922), this time a physician at the Mayo Clinic, published a paper on what he called 'Hysterical Dysphagia'. This was primarily an affliction of women and it was noticeable that 37 of his 63 patients had hæmoglobin values of less than 60%. It has since become reasonably evident that he was describing precisely the same clinical condition as were his British contemporaries; which makes it all the more surprising that he failed to note any of the abnormal changes on endoscopy of the pharynx or lesions of the mouth and tongue to which Paterson and Brown-Kelly had paid so much attention. This absence of any evident organic disease in the upper food passages led him to the conclusion that the dysphagia was an hysterical manifestation. This view was not supported by Paterson and Brown-Kelly, who considered that the dysphagia was due to spasm consequent on the local anatomical changes present at the site of obstruction.

It was on the basis of this communication alone that Vinson has come to enjoy eponymous dis-

inction. More fortunate still is Plummer, a physician colleague at the Mayo Clinic, who does not seem to have made any literary contribution on this topic and to whose interest in the condition Vinson only made passing reference in his paper. In the discussion which followed the presentation of Vinson's paper it was suggested that 'because of the fact that no other clinic has recognized this disease, it seems only fair that Dr. Vinson's name should be given to this disease'. However, not all the audience were so benevolent, for when Dr. S. H. Boyer, of Duluth, remarked, 'the multiplicity of personal names for disease is wrong; let us not add to this but let us distinguish the doctor (Vinson) in some other manner', we are informed that his comment was greeted by applause. It must, none the less, be admitted that however strong may be our claim for the British contributors on the score of priority, we will find it hard to win a place for Paterson and Brown-Kelly. Plummer-Vinson syndrome it is, and so it is likely to remain.

It is largely to the contributions of the Scandinavian and particularly of the Swedish writers that we are indebted for our more complete understanding of this disease, if disease it deserves to be called. It is evident that there is, in Sweden, a remarkable incidence of this condition amongst the female population although in the other Scandinavian countries and in Great Britain, North America and Australia it is much less common.

The disease is almost always confined to females of middle age (contrast Figs. 1 and 2). The dysphagia, usually referred to the level of the larynx, is often of many year's duration and insidiously progressive. There is often complete edentia, a tight and smooth facial skin, a small mouth fissured or scarred at the angles, and fingernails which are usually brittle and sometimes spoon-shaped (Fig. 1). We note that

*FIG. 1.—Severe koilonychia and irregularity of the nails in male patient with Plummer-Vinson Syndrome.

*FIG. 2.—(Same patient as Fig. 1.) After iron therapy for one year, the nails have become normal.

*Figures 1 and 2 reproduced with the kind permission of Professor Jacobson of the Radiumhemmet, Stockholm.

similar changes are seldom described in the toenails, nor have we observed them. The buccal mucosa is pale, atrophic and often the seat of leukoplakia; the tongue is atrophic and red (Fig. 3). Similar changes are evident in the pharynx and œsophagus and are often associated with fibrous bands or web-like strictures in the lower pharynx or upper œsophagus (Fig. 4). Atrophy of the gastric mucosa is often present and usually associated with achlorhydria. The spleen is palpable in about 20% of cases. Many

patients have an associated hypochromic microcytic anemia, but its absence is not uncommon.

This is the clinical picture presented by a patient with severe long-standing disease. But it is important to remember that the clinical features are often much less evident. Most important of all we have now come to recognize that anemia is very often not in evidence.

It is now agreed that the Plummer-Vinson syndrome is the sequel of a long-standing depletion of body iron stores and there are two features of

FIG. 3.—(Case 5) Atrophic mucosa and superficial ulceration of the tongue. The area of scarring on the left side of the dorsum of the tongue was the site of a squamous cell carcinoma treated by radon seed implantation three months previously

FIG. 4.—A thin fold in the upper oesophagus, arising anteriorly and stretching across the lumen—a typical web.

the condition which are usually regarded as being essential for its diagnosis. They are, firstly, dysphagia associated with the characteristic mucosal lesions, and secondly, evidence of diminished body iron stores usually associated with low serum iron values and absence of stainable iron in the bone-marrow. It was the constant presence of these two features that led Waldenstrom and Kjellberg (1939) to introduce the term 'sideropenic dysphagia' to describe the condition; this is a much more informative title and its use dodges the controversy in the eponymous description of this syndrome that has taken place over the years. In a recent review of Swedish cases, however, Wynder and Fryer (1958) state that many female patients, having the classical clinical stigmata of the Plummer-Vinson syndrome with or without cancer, have normal serum iron and hæmoglobin values when first seen. This somewhat surprising observation they attribute to the fall in iron requirements that follow the cessation of menstruation, the persisting tissue changes being presumably irreversible.

It was probably Logan Turner, of Edinburgh, who was the first to observe, in 1913, the neoplastic potential of the mucosal lesions seen in this syndrome. He described 68 cases of malignant disease of the œsophagus and remarked on the greater female incidence of carcinoma at the upper end compared with other levels in the œsophagus. He also commented on the often prolonged history of dysphagia in many of these women with carcinoma, and stated: 'These cases sufficiently illustrate the period over which symptoms produced by undoubted malignancy of the œsophagus may continue'. The average duration of the dysphagia in Logan Turner's female patients with hypopharyngeal carcinoma was five years. By 1920 Logan Turner had extended his observations to 140 cases of œsophageal carcinoma, 98 of whom were hypopharyngeal. Of these 98, no less than 85 occurred in females. Whereas, in males, the average duration of the dysphagia was but a few months, the dysphagia in the females had in some cases been present for many years. Being by then aware of the writings of Paterson and Brown-Kelly, Logan Turner wrote: 'In most women whose period of symptoms is unusually prolonged, it is possible that a condition may exist which favours tumour development and is the cause of the obstruction in the earlier stages of the history'. Because of these observations, there seems little doubt that many of Logan Turner's patients had suffered from the Plummer-Vinson syndrome or sideropenic dysphagia. Paterson, in 1919, had remarked on '... the not infrequent supervention in such cases of malignant disease at the mouth of the gullet', and Brown-

Kelly had noted a striking female sex preponderance in his cases of hypopharyngeal carcinoma.

It had thus become clearly apparent by this time that patients with the Plummer-Vinson syndrome often developed hypopharyngeal or, as it is more often called, post-cricoid carcinoma.

However, it was not until 1936 that H. E. Ahlbom, from observations at the Radiumhemmet in Stockholm, produced convincing evidence of the development of cancer of the hypopharynx in patients with the Plummer-Vinson syndrome.

When in 1937 Ahlbom examined the records of all the women treated at the Radiumhemmet for meso- and hypopharyngeal carcinoma from 1931 to 1936, he found that the Plummer-Vinson syndrome was present in no less than 90%. But he was also able to show from his experience (and this is an important fact which is often overlooked) that the risk of cancer developing was not confined to the post-cricoid area but affected also the buccal mucosa, tongue, and all levels of the œsophagus.

The incidence of the Plummer-Vinson syndrome in Australia is probably little different from that which obtains in the United Kingdom or in the North American continent and, largely due to its infrequency, figures for its incidence are not readily obtainable. We have, however, been able to lay hands on a limited number of figures of the incidence of upper gastro-intestinal tract carcinoma reported at the Central Cancer Registry, Melbourne, in the years 1950 to 1954, and to compare them with the number reported from hospitals in Sweden, Denmark, the United Kingdom and the United States during the same period (Table I).

The figures for Melbourne reveal approximately the same sex incidence as was observed in Denmark, the United Kingdom and North America; in contrast are the figures for Sweden which reveal a striking female incidence, especially at hypopharyngeal level.

Vidboek, in 1944, reviewed 1,313 cases of upper alimentary tract carcinoma in Denmark. The incidence of carcinoma of the pharynx and œsophagus in females was only half that of Swedish women and this he attributed to the lower incidence of Plummer-Vinson syndrome in Danish as compared with Swedish women. Only six of his patients, all female, had evidence of this syndrome.

There is, therefore, reasonably convincing evidence that in women the Plummer-Vinson syndrome is an important ætiological factor in the causation of cancer of the mouth, pharynx and œsophagus. Certainly the incidence of cancer at these sites in women parallels fairly closely the

TABLE I
NUMBER OF CANCER PATIENTS AND PERCENTAGE OF WOMEN WITH CANCER, BY SITE, AT HOSPITALS IN AUSTRALIA, SWEDEN
DENMARK, ENGLAND AND THE UNITED STATES DURING 1950-1954

Site	Australia Melbourne		Sweden Radiumhemmet		Denmark Radium Centre		England Royal Marsden		United States Memorial Centre	
	No. Patients	% Women	No. Patients	% Women	No. Patients	% Women	No. Patients	% Women	No. Patients	% Women
Lip	334	19	249	9	200	12	33	15	219	7
Buccal Mucosa	9	22	74	51	34	35	16	25	8	37
Gingiva	13	31	64	47	34	53	13	38	207	26
Palate	26	27	28	50	27	37	31	19	160	23
Tongue	94	27	164	45	99	41	82	22	549	30
Tonsil	36	17	31	29	29	24	40	25	178	16
Naso-pharynx	14	50	113	42	31	26	72	25	154	27
Hypo-pharynx	49	35	157	57	60	18	118	30	349	8
Oesophagus	176	30	259	39	213	28	83	32	308	16

(Based on Wynder, Hultberg, Jacobsson and Bross (1957))

frequency of the Plummer-Vinson syndrome, and this is strikingly borne out by the Swedish figures. In spite of the relative infrequency of this syndrome in Australia we have within recent times treated patients suffering from cancer of the upper gastro-intestinal tract, each of whom had some or all of the stigmata of the Plummer-Vinson syndrome. It seemed to us not inappropriate to give a short account of these five cases in an attempt to underline the importance of this syndrome as an ætiological factor in the causation of mouth cancer and the need to be constantly on the look-out for this complication in any patient with a long history of dysphagia with or without iron-deficiency anaemia.

Case Reports

CASE 1—Carcinoma of the Alveolus, Tongue, Palate, Hypopharynx

Mrs. C. H., an English migrant aged 65 years, was admitted to the Alfred Hospital in December 1960, under the care of Dr. J. Stubbe. Five years before, whilst an inpatient in the London Hospital, she had complained of dysphagia and ulcers in the mouth of ten years duration. She was then found to have the characteristic facies of the Plummer-Vinson Syndrome and her fingernails were flat and ridged. There was an ulcerating tumour involving both the floor of the mouth and the left mandible which was proven on biopsy to be an early infiltrating squamous cell carcinoma. Because of an extensive tissue reaction which developed before a course of radiotherapy could be completed, surgical excision of the tumour and left half of the mandible was performed. Apart from continuing mild dysphagia she had re-

mained well following this operation but was admitted to the Alfred Hospital with a short history of weakness, dyspnoea, weight loss and increasing dysphagia. She was pale and thin and had scarring at the angles of the mouth and leukoplakia of both upper and lower lips. Her operation scar was well healed and there was no hint of local or cervical lymph node recurrence. The buccal mucosa was pale and atrophic and the gums edentulous. The tongue was atrophic, bled easily and was surmounted by multiple white flat plaques 3 to 4 mm. in diameter (Fig. 5). There was an irregular penetrating ulcer 1 cm. in diameter on the soft palate. Her fingernails were brittle and ridged but not spoon-

FIG. 5.—(Case 1) Multiple raised plaques on the tongue which, on biopsy, proved to be squamous cell carcinoma.

shaped; the spleen was not palpable but the liver was enlarged and irregular.

Investigations. Hæmoglobin 8 g./100 ml.; blood film, hypochromic anæmia; serum iron, 25 µg./100 ml.; stools positive for occult blood. Œsophagoscopy (Mr. G. Stirling): at 14 cm. from the alveolar margin there was a friable, fungating annular tumour preventing entry to the Œsophagus. Biopsies of the lesions on the tongue, palate and hypopharynx showed well differentiated squamous cell carcinoma. Biopsy of the buccal mucosa showed atrophy with submucosal inflammatory cell infiltration.

A palliative course of radiotherapy was prescribed.

CASE 2—Carcinoma of the Hypopharynx

Mrs. E. B. aged 65 years was admitted to the Royal Melbourne Hospital on April 14, 1960, under the care of Professor R. R. H. Lovell.

From the age of 40 years or thereabouts she had experienced difficulty in swallowing, solid food appearing to stick at the level of the supra-sternal notch. During the previous year, she had become progressively more tired and short of breath on exertion. The dysphagia had increased in severity in the past three weeks.

Examination revealed a thin, pale woman with koilonychia and brittle nails. She was edentulous and had a red atrophic tongue and cracking at the angles of her mouth. The spleen was palpable.

Investigations. Hæmoglobin 5.9 g./100 ml.; blood film, erythrocytes hypochromic with anisocytosis; colour index 0.46; serum iron 16 µg./100 ml.; occult blood negative; bone marrow, hyperplastic with no stainable iron. X-ray: Barium swallow demonstrated an extensive irregular tumour of the hypopharynx extending into the upper Œsophagus. This on biopsy proved to be a squamous cell carcinoma and a section taken from the mucosa adjacent to the lesion showed quite striking hyperkeratotic changes.

Operative treatment was considered inadvisable because of her poor general condition and she died two weeks after admission despite blood transfusion.

Autopsy revealed an extensive carcinoma of the hypopharynx extending into the upper Œsophagus (Fig. 6). There were metastases present in adjacent lymph nodes and in the liver.

CASE 3—Carcinoma of the Buccal Mucosa

Mrs. J. B., aged 63 years, was admitted to the Royal Melbourne Hospital on October 19, 1956, under the care of Professor M. R. Ewing. For as long as she could remember she had found difficulty in swallowing solid foods. For one month she had suffered with tiredness and a painful tongue and recently a small ulcer had appeared near her lower gum.

She was a thin edentulous woman with atrophic glossitis and some small areas of leukoplakia on the lower alveolus. She had a firm, raised circular ulcerated lesion 3 cm. in diameter in the right lower gingivobuccal sulcus encroaching on the right alveolus (Fig. 7). A single hard lymph node 1 cm. in diameter was palpable in the right submandibular region.

Investigations. Hæmoglobin 13 g./100 ml.; blood film normal; W.R. negative. X-ray: Barium swallow revealed a web in the lower cervical Œsophagus. Biopsy of lesion: squamous cell carcinoma of the buccal mucosa.

On October 10, 1956, an excision of this lesion with the right half of the mandible and a right-sided block dissection of the neck was performed. She remained well until January, 1957, when a left-sided submandibular

FIG. 6.—(Case 2) Autopsy specimen showing an extensive carcinoma of the hypopharynx and carcinoma of the upper Œsophagus.

recurrence necessitated a left-sided block dissection of the neck.

Ten months after the original excision she again presented with a recurrence in the right parotid gland. A course of deep X-ray therapy was commenced but she deteriorated and died on September 1, 1957.

Autopsy revealed secondary squamous cell carcinoma in the right parotid gland.

FIG. 7.—(Case 3) Carcinoma of the buccal mucosa.

CASE 4—Carcinoma of the Oesophagus

Mrs. M. M., aged 60 years, was admitted to the Alfred Hospital on March 1, 1957, under the care of Professor M. R. Ewing. For 17 years she had been unable to eat solid foods because of obstruction to swallowing at the level of the manubrium sterni. For five weeks she had suffered from lower sternal discomfort on eating, pain under the left costal margin, regurgitant vomiting, anorexia and loss of weight. Some years previously she had been given a blood transfusion because of anaemia.

Examination revealed a thin, pale, edentulous woman with a small mouth with angular scarring. She had a raw, smooth tongue and koilonychia.

Investigations. Haemoglobin 9.7 g./100 ml.; blood film, hypochromic red cells with anisocytosis; serum iron 35 µg./100 ml. X-ray: Barium swallow revealed partial obstruction to the passage of barium due to a web at the level of the sixth cervical vertebra. There was also dilatation of the middle third of the oesophagus and an irregular stricture in the lower third. Oesophagoscopy (Mr. K. N. Morris): The entrance to the oesophagus was difficult to identify and a lesion in the nature of a web was ruptured before entering the oesophagus. At 35 cm. a fungating tumour was visualized. Biopsy of this lesion proved it to be a well differentiated squamous cell carcinoma.

On March 21, 1960, a partial oesophago-gastrectomy was performed by Mr. K. N. Morris. The resected specimen revealed an extensive squamous cell carcinoma of the lower third of the oesophagus without spread to adjacent lymph nodes.

Now three and a half years later she remains well despite some mild residual dysphagia.

CASE 5—Carcinoma of the Tongue

Mrs. E. S., aged 64 years, was admitted to the Alfred Hospital on March 3, 1960, under Dr. J. McLean. For the past 17 years she had suffered with dysphagia, recently increasing in severity. Over this period a typical Raynaud's phenomenon had affected her hands and feet on exposure to cold. She had suffered for many years from anaemia resistant to treatment with Vitamin B₁₂. Over the previous year she had suffered from anorexia, mild loss of weight and a painful tongue.

Examination revealed a well nourished woman with sclerodactyly, brittle nails and tight, smooth facial skin. There was scarring at the angles of the mouth and a raw smooth tongue with shallow and non-indurated ulceration on the left side of the dorsum measuring 1 cm. by 2 cm. in diameter (Fig. 3). There was no palpable cervical lymph nodes.

Investigations. Haemoglobin 13.8 g./100 ml.; blood film normal; serum iron 40 µg./100 ml.; Wassermann negative; Schilling test normal; Histamine test meal, achlorhydria; stools negative for occult blood. X-ray: barium swallow revealed a small web in the post cricoid region. There was also dilatation of the lower third of the oesophagus and a stricture at the lower end. Oesophagoscopy: fibrous stricture 5 mm. in diameter dilated at pharyngo-oesophageal junction. Benign stricture at lower end of oesophagus. Gastric mucosa atrophic. Biopsy of ulcer on tongue: well differentiated squamous cell carcinoma.

The dysphagia was subsequently relieved by the regular passage of bougies. In June, 1960, radon seeds were implanted into the tongue lesion after she had refused any major operative procedure.

Discussion

The important points that now emerge for discussion are:

- (a) What is the aetiology of this condition?
- (b) What is the nature of the lesions in the upper alimentary tract?
- (c) Is the condition preventable or are the established lesions reversible?

(a) What is the aetiology of this condition?

As in the case with many other disease complexes, controversy has existed over the true aetiology of this syndrome.

Streptococcal infection (Hurst, 1926), tertiary syphilis, vitamin deficiency, hysteria (Vinson, 1922), and 'gastric inadequacy' (Suzman, 1933) have all, at some time, been suggested as possible causes. Dysphagia was once considered to be the primary factor, the resulting inadequate oral intake being held responsible for the secondary deficiencies. The passage of oesophageal bougies alone, however, although it may be effective in the relief of dysphagia and in the amount and variety of oral intake, has been shown to lead to little or no improvement in the condition (Johnson, 1931). The commonly associated achlorhydria and gastric atrophy led to the suggestion that the primary defect was that of 'gastric inadequacy'. It has, however, subsequently been shown that the presence of acid in the stomach is only of minor

importance in iron absorption. Nevertheless, it may assume greater importance when the iron in the diet is only just sufficient for daily needs. Witts (1931) treated his patients with liver, hydrochloric acid and multiple vitamins and found that the lesions did not improve. This was in direct contrast to the rapid response with iron therapy. Treatment with riboflavine alone has been found to improve only the oral fissures (Hurst, 1926).

There is now little doubt that the degenerative changes in the mucous membranes of the upper gastro-intestinal tract associated with the Plummer-Vinson syndrome are primarily caused by a prolonged iron deficiency. Most of the evidence for this has been of an indirect nature, that is the observed resolution of many of the lesions with iron administration (Witts, 1931; Suzman, 1933; Andersson, 1955; Waldenstrom, 1938). Vinson (1922) had treated his dysphagic female patients with iron, arsenic, and oesophageal bouginage and remarked on the rapid improvement in the symptoms and blood picture. There is good evidence that iron usually produces a rapid resolution of the nail and epithelial changes (Figs. 1, 2), but less often is there any lessening of the dysphagia.

It is observed that this syndrome occurs almost always in females and rarely in males. This is readily explained by the increased iron requirements of the female during menstruation, pregnancy and lactation. Many of these women live on a diet which is marginal in iron content and the increased requirements during reproductive life predispose to the development of iron deficiency. Since 1938 the Swedish Public Health Service has sponsored the fortification of white flour with iron and vitamin B, and '... it is now a widely held clinical impression in Sweden that Plummer-Vinson syndrome is becoming a progressively rarer entity' (Wynder and Fryer, 1958).

It is believed that iron deficiency produces a generalized disturbance affecting the whole organism and that the deficiency is most evident in the tissues where cells are constantly being regenerated (Demulder, 1958). Changes are readily observed, for example, in the bone-marrow (disturbed cell maturation), skin and its appendages (koilonychia, smooth facial skin with oral angular fissures), and mucous membranes (buccal cavity, tongue, pharynx, oesophagus, stomach). The small intestinal mucosa, where mitosis is so active, however is usually not affected (Rawson and Rosenthal, 1960).

Iron is present in the body chiefly as hæmoglobin and myoglobin, but is also an essential component of the intracellular enzymes catalase, peroxidase and the cytochromes. All these enzymes play an essential role in the transport and utilization of oxygen for energy requirements.

Beutler (1957, 1959) has shown experimentally that, in rats made iron deficient by bleeding, specific intracellular iron-containing enzyme deficiencies occur in some organs. These enzyme deficiencies have not been shown to occur in the altered mucosal cells in human patients with chronic iron deficiency, but metabolic studies of excised 'precancerous' leukoplakic mucosa suggest an abnormal pattern of oxidative mechanism before carcinoma develops (Weisberger, 1957).

If these deficiencies of iron-containing enzymes do in fact occur, the subsequent neoplastic change in the mucosa may be explained by the theory of Warburg (1956), who states that the first phase in the origin of a carcinoma cell is the irreversible injuring of respiration followed by a long struggle for existence of injured cells, those surviving replacing the lost respiration energy by fermentation energy and, in so doing, becoming de-differentiated to a neoplastic cell.

(b) *What is the nature of the lesions in the upper alimentary tract?*

The microscopic features of the atrophic mucous membranes seen in this disease were first described by Paterson (1919) and later by Suzman (1933).

In general, all the epithelium from the mouth to the lower oesophagus is atrophic but, in many areas, shows evidence of increased cellular activity in the basal layers with superficial hyperkeratosis or leukoplakia (Figs. 8, 9) (similar to the skin lesion seen after initial applications of a carcinogen).

The tongue mucosa is usually smooth and devoid of papillæ (Fig. 3). Throughout the areas of atrophic mucosa there is submucosal infiltration with inflammatory cells. In the oesophagus this infiltration often extends into poorly developed muscle coats which are often partly replaced by connective tissue (Fig. 8). In addition, further changes commonly occur in the lower pharynx or upper oesophagus. Most frequently this is the characteristic and often radiologically demonstrable web, a thin fold usually arising anteriorly and stretching a variable distance across the oesophageal lumen (Fig. 4). Hoover (1935) biopsied these webs and found them to be composed of two mucous membrane layers with minimal intervening fibrous tissue. The obstructing lesion is often more extensive—either a narrow circular constriction of the lumen or rarely an elongated oesophageal stricture. There is commonly present an associated atrophy of the gastric mucosa with submucosal cellular infiltration. However, the small intestine shows no macroscopic or microscopic changes (Rawson and Rosenthal, 1960).

The neoplastic changes that commonly arise

FIG. 8.—(Case 4) Biopsy of the oesophagus. Leukoplakia of the oesophageal mucosa and submucous infiltration with inflammatory cells extending into the muscle coat. ($\times 120$)

FIG. 9.—Biopsy of buccal mucosa in Plummer-Vinson Syndrome. Leukoplakia of the mucous membrane. Submucous inflammatory cell infiltration. ($\times 170$)

in the mucosa at any level from the mouth to the lower œsophagus are stated to occur in approximately 10% of patients with established Plummer-Vinson syndrome (Wynder, Hultberg, Jacobsson and Bross, 1957), most commonly at hypopharyngeal level but sometimes simultaneously at multiple sites (as in Case 1). The carcinoma developed is always of squamous-cell variety but with varying degrees of differentiation.

After a study of patients developing carcinoma in association with web and stricture formation, Lindvall (1953) concluded that malignant degeneration did not occur at the site of these structural changes but in areas adjacent to them.

(c) Is the condition preventable or are the established lesions reversible?

Many writers have commented on the reversibility of many of the lesions of Plummer-Vinson syndrome following the administration of iron. If anæmia is present there is an immediate hæmatological response—the fingernails become normal (Figs. 1, 2) and even the atrophic lingual and buccal mucosa may be restored to normal.

The commonly present achlorhydria, especially in older women, is not reversible (*Lancet*, 1960). Lees and Rosenthal (1958) carried out gastric biopsy before and after correction of the blood picture with iron in patients with iron deficiency anæmia and found that the gastric mucosal lesions of infiltration and atrophy did not improve, and in some cases progressed.

Dysphagia may be improved following the administration of iron even without œsophagoscopy or bouginage but, if any radiological changes are present in the œsophagus, these usually persist.

However, it is a common observation that somewhere in the course of the disease the characteristic mucosal lesions become irreversible, even with prolonged treatment. It is probable then, that only in the early stages of the disease when the epithelial lesions are reversible, can therapy with iron prevent the later malignant changes. Weisberger (1957) stated that the treatment of the anæmia in 18 cases with Plummer-Vinson syndrome had no effect on the eventual development of carcinoma. Also, of eight patients with this syndrome observed by Lindvall (1953) and known to have had previous iron therapy, seven developed carcinoma at some later stage in the disease.

We may then argue that a prolonged iron deficiency 'conditions' the mucosa of the upper gastro-intestinal tract producing a neoplastic potential which at some stage becomes irreversible. The prevention of this irreversible change would then depend ideally on the prevention of iron deficiency or, if iron deficiency

occurs, on its early diagnosis and on the continued replenishment of the depleted iron stores. There is as yet no evidence to prove whether or not the incidence of subsequent neoplasia can be influenced by adequate iron therapy once irreversible, but still benign changes have occurred. Therefore, energetic treatment which in any event improves many of the symptoms associated with the Plummer-Vinson syndrome should be instituted in all cases.

Endoscopic examination of the œsophagus is essential in all patients, and for three reasons: (1) to exclude other causes of the dysphagia; (2) to exclude any malignant change in the œsophagus; and (3) therapeutically to improve the dysphagia which is often severe and distressing. Even apparently innocent lesions should be biopsied. In one of our patients carcinoma of the tongue was discovered on biopsy of a non-indurated superficial ulceration.

Because of the risk of the development of cancer, all patients with the Plummer-Vinson syndrome should be kept constantly under review so that if malignant change occurs, early diagnosis and treatment can be instituted.

Summary

It is now reasonably evident that the changes observed in patients with Plummer-Vinson syndrome (or sideropenic dysphagia) are caused by long-standing depletion of body iron stores. The evidence for this is, firstly, the diminished marrow and serum content of iron, and secondly the observed retrogression of many of the classical features of the disease following the therapeutic administration of iron. It is important to realize that anæmia may be absent, even in long-standing disease.

Invariably there are atrophic mucous membrane changes present throughout the upper gastro-intestinal tract and, in the early stages of the disease, these changes are reversible with iron administration. However, in the absence of treatment, these mucosal changes become irreversible and, in many patients, malignant degeneration occurs. This malignant change can occur not only at hypopharyngeal level but at any or multiple sites in the mouth, tongue, pharynx or œsophagus.

Diagnosis should be possible before these irreversible changes have occurred and, at this stage, the later malignant changes can be prevented by continued replenishment of the iron stores. If long-standing disease is present, the possibility of later malignant change must be borne in mind so that early diagnosis and treatment can be instituted.

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