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THE PATERSON-BROWN KELLY SYNDROME

ITS RELATIONSHIP TO IRON DEFICIENCY AND POSTCRICOID CARCINOMA

PART I

By R. F. McNAB JONES (Manchester)

THIS syndrome, in which dysphagia is associated with hypochromic anæmia, has been well known under a variety of names, for the past forty years. A considerable volume of literature on the subject has been published during that time and this is reviewed under various headings.

General Survey of the Literature

Although other writers had previously described some features of the condition, Paterson and Brown Kelly at a meeting of the Royal Society of Medicine in 1919 gave the first comprehensive description of the syndrome. Their names have been attached to the syndrome in this country, but in the United States of America it is usually referred to as the Plummer-Vinson syndrome, while in Scandinavia the term *sideropenic* dysphagia is used. Plummer partially described the syndrome in 1914 and Vinson amplified this description in 1922—they both believed the dysphagia was an hysterical manifestation. The term sideropenic dysphagia was suggested by Waldenstrom (1938), who believed the basic cause was iron deficiency.

Studies on series of these patients confirmed the original findings, viz: 1926, Moersch and Conner; 1927, Brown Kelly; 1928, Jones and Owen; 1929, Cameron; 1931, Paterson; 1932, Graham and Johnson.

In 1936 Ahlbom published an investigation of 150 cases of carcinoma

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of the upper alimentary tract in women and showed a high proportion of them had a preceding Paterson-Brown Kelly syndrome.

Other writers (Simpson, R. (1939), Videback (1944), author (1957)) have pointed out that multiple primary carcinomata may develop anywhere in the upper alimentary tract in these patients.

Owen (1950) gave a comprehensive review of the relationship between the Paterson-Brown Kelly syndrome and postcricoid carcinoma.

Until 1940 the great majority of papers on the subject had come from the United States, Scandinavia and Great Britain. It was believed at that time that the condition had a racial incidence, being found mainly in those of Anglo-Saxon descent, and that it was more or less unknown in Latin, Slav and Asiatic countries. Since then, however, a considerable number of papers on the condition and descriptions of cases have appeared in journals in France, Italy, Belgium, Poland, Spain, Holland, Czechoslovakia and South America. (See references Appendix 1.) The general opinion as expressed in these papers is that the condition is by no means as rare in these countries as had previously been thought and that many cases had probably been missed in the past.

Description of the Syndrome

A well developed case presents a typical picture.

The patient is usually a small, "shrunken" middle-aged female.

She gives a history of difficulty in swallowing, mainly for solids, and this "small swallow" has often been present for as long as she can remember. As a result, the diet is semi-solid with a high carbohydrate and low protein content. Many patients have had an incident in the past when a solid particle, such as a piece of meat or nut has got stuck in the upper gullet, and the resultant choking fit has made them nervous, slow eaters.

In addition to the dysphagia, many of these patients will give a history of anæmia and complaints of soreness of the tongue and mouth, flatulence and dyspepsia are common. A few also suffer from diarrhœa and paræsthesiae.

On clinical examination koilonychia, cheilosis and edentia are usually obvious, while dryness of the skin and dry, brittle hair are noted in many cases. The tongue is smooth and red and the mucosa of the pharynx as seen with the laryngeal mirror may appear pale and atrophic. Splenomegaly and sometimes hepatomegaly may be present.

The blood picture is that of hypochromic microcytic anæmia, though in a few recorded cases hyperchromic anæmia has been found.

Gastric analysis shows complete achlorhydria in many cases.

Barium swallow examination may reveal a web formation in the hypopharynx or an area of constriction several centimetres in length in the same region.

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Direct pharyngoscopy may show atrophic mucosa in the hypopharynx, fissures and slight superficial ulceration. A web, if present, is seen as a thin, crescentic membrane, usually arising from the anterior or lateral walls of the hypopharynx and stretched across the lumen which is narrowed to a variable extent. Alternatively, there may be a marked narrowing of the gullet for several centimetres at the same level.

In one recorded case with persistent diarrhœa sigmoidoscopy revealed atrophic changes in the mucosa of the colon (Graham and Johnson, 1932).

In another single recorded case with very severe iron deficiency anæmia there were vaginal changes similar to those seen in the mouth and pharynx (Ezes, H. 1951).

Incidence of Stigmata in Paterson-Brown Kelly Syndrome

Few cases of this syndrome will exhibit all the symptoms and signs described above. In order to diagnose the condition, only dysphagia with some of the accompanying signs and symptoms is necessary. An analysis of the incidence of the accompanying stigmata in four different series of cases is given below.

TABLE I.

	No. of Cases	Dysphagia	Glossitis	Cheilosis	Anæmia	Achlorhydria	Koilonychia	Splenomagaly	Abnormal Ba. Swall.
		%	%	%	%	%	%	%	%
Moersch & Conner (U.S.A.) 1926	65	100	15	Common	100	80 in 10 cases	—	30	—
Sotgiu & Labo (Swiss) 1956	37	100	5	70	41	84	40	—	40
Wynder *et al.* (Sweden) 1958	150	100	38	62	77	—	38	—	—
Author (1959)	94	100	70	38	100	90	50	23	50 of 39 cases

Averaging up the findings in these four series it will be seen that the stigmata occur in the following order of frequency: Anæmia and Achlorhydria in approximately 80-90 per cent., Cheilosis 60-70 per cent. Glossitis 50-60 per cent., Koilonychia 40-50 per cent., Splenomegaly 20-30 per cent. In addition about half the cases will show abnormalities on barium swallow examination.

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Incidence of Stigmata in Hypochromic Anæmia

If one considers all cases of hypochromic anæmia, then the various stigmata occur with the following frequency according to two recorded series. As will be seen, dysphagia occurs in 10-13 per cent. of all cases of hypochromic anæmia.

TABLE II.

	No. of Cases	Dys-phagia	Achlor-hydria	Glossi-tis	Spleno-megaly	Koilo-nychia
		%	%	%	%	%
Davidson, 1938	125 (severe)	10	66	30	27	17
Witts, 1931	117	13	81	50	30	—

Screening 2,012 cases of hypochromic anæmia seen in the Hæmatology Department of Manchester Royal Infirmary produced 106 cases with dysphagia, an incidence of 5 per cent.

Associated Syndromes

Sjogren's syndrome is found in post-menopausal women. It consists of polyarthritis and failure of lacrimal and salivary secretion due to disintegration of the parenchyma of the affected glands. The lack of secretion leads to "dry eyes" and dryness of the mouth and throat.

Godtfredsen (1947) investigated 23 cases of this syndrome and found evidence of Paterson-Brown Kelly syndrome in 13 cases. The majority of these had iron deficiency anæmia and achlorhydria and 3 showed a web formation on barium swallow examination.

Flusser *et al.* (1954) believes Sjogren's syndrome and Paterson-Brown Kelly syndrome are two manifestations of a similar deficiency disease and describes them as the sialopenic and sideropenic forms respectively.

Hunner's ulcer of the bladder may possibly be related to the Paterson-Brown Kelly syndrome. Robb (1941) reports two cases of the former conditions, both showing marked iron deficiency anæmia and one having a well-developed Paterson-Brown Kelly syndrome and a history of a previous pre-cancerous lesion in the mouth.

Ætiology of the Syndrome

Many different theories have been advanced for the causation of the syndrome.

In particular three causative factors have received considerable support from writers on the subject namely (1) primary dysphagia, (2) riboflavin deficiency, and (3) iron deficiency.

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(1) *Primary Dysphagia.*

Those who support this theory believe that the dysphagia, due to a "stricture" in the hypopharynx, causes the patient to modify her diet, producing iron and vitamin deficiencies which result in the development of hypochromic anæmia and the other stigmata of the condition.

Most of the early writers on the subject believed in this sequence of events. Bronner (1913) ascribed the development of the hypopharyngeal stricture to the repeated trauma of swallowing a hard bolus, while others (Jones and Owen (1928), Kelly (1919), Moersch (1926), McKenzie (1918) and Paterson (1919) believed it was due to spasm, and Plummer (1914) and Vinson (1922) thought it was an hysterical manifestation. Hurst (1926) believed streptococcal infection caused the narrowing of the hypopharynx.

By 1937, however, Paterson had doubts that the dysphagia was the primary change and he then emphasized the importance of iron therapy.

(2) *Riboflavin Deficiency*

The buccal and tongue changes and the angular stomatitis seen in this syndrome suggested a riboflavin deficiency. Simpson, J. (1939), Videback (1944), Pollack (1945) and Savilahti (1946) all believe that riboflavin deficiency plays an important rôle in the development of the syndrome. Ferrando-Botet (1949) suggests that it is a lack of Vit. B_2 complex which is particularly important.

Murphy (1940), Jankelson (1940) and Meulengracht (1941) report cases of the syndrome successfully treated with riboflavin.

Franschetti (1943) treated cases of Sjogren's syndrome with Vit. B complex with favourable results.

Against this theory is the fact that cases of true riboflavin deficiency as described by Jehgers (1942) differ from the Paterson-Brown Kelly syndrome in that ocular manifestations are common, while dysphagia is rare. The tongue is a magenta-colour, unlike the smooth, red tongue seen in Paterson-Brown Kelly syndrome.

(3) *Iron Deficiency*

The majority of writers on the subject in recent years have considered a primary iron deficiency as the basic cause. They believe this can lead to changes in the mucosa of the upper alimentary tract and to dysphagia. The iron deficiency also causes hypochromic anæmia, angular stomatitis and koilonychia, and may be responsible for atrophic changes in the gastric mucosa. They accept the fact that there may also be some degree of riboflavin deficiency, probably as the result of the modified diet.

Leblond and Stevens (1948) have shown that the surface cells in the intestinal epithelium of rats are renewed every one and a half days.

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Iron and riboflavin are important for the formation of cellular enzyme systems, and it is thought that a lack of these substances can interfere with cellular regeneration in the epithelium of the upper alimentary tract. Cojazzi (1949) claims to have confirmed this experimentally. Cordray (1940) fed rats on an iron-free diet and produced histological changes in the mucosa of the gullet, but noted no submucosal fibrosis.

Many writers (Cahn (1952), Cameron (1929), Henderson (1954), Hoover (1935), McGibbon (1935) and Witts (1956)) believe that iron deficiency is the basic cause, although Ahlbom (1936) thinks the condition may differ in some respects from the normal hypochromic anæmia, and Graham and Johnson (1932) noted an increased fragility of red cells in five out of their six cases.

It was Waldenstrom in 1938 who first suggested that the changes in the mucosa and nails could occur without anæmia, but with a low serum iron, and that iron therapy alone would cure many cases and reverse the epithelial and nail changes. For this reason he suggested the condition be named sideropenic dysphagia.

In 1944 Glazebrook described a case of polycythæmia rubra vera who had a low serum iron and koilonychia. He believed the sideropenia was due to the excessive demands for iron for hæmoglobin formation. After treatment by irradiation of the bone marrow the serum iron rose from 50 micrograms per 100 ml. to 320 micrograms per 100 ml., and the koilonychia recovered.

Darby (1946), in a convincing article on the causation of the oral lesions in hypochromic anæmia, details six such cases, two of which also had dysphagia. Four of these failed to respond to Vit. B therapy, while all responded satisfactorily to iron therapy alone. He was careful to see that the patients' diets remained unaltered during treatment. He points out that one may get oral lesions in hypochromic anæmia without dysphagia and with an adequate diet. Also, that in most nutritional surveys the oral lesions have been found to be associated more commonly with low hæmoglobin levels than with Vit. B. deficiency.

Sacrez *et al.* (1954) records an interesting case of a child four years of age who had œsophageal strictures, one in the middle and one in the lower third of the gullet, probably congenital in origin. As a result, the diet was entirely fluid from birth and when first seen the child was pale and wasted with marked glossitis and a hæmoglobin level of 30 per cent. Dilatation of the strictures allowed a normal diet to be taken, but no improvement was noted in the blood picture or the glossitis and the child continued to complain of some dysphagia. Iron therapy was started and within two months the hæmoglobin level was 70 per cent. and the glossitis and dysphagia had completely resolved, although barium swallow examination showed very little change in the strictures.

Sotgiu and Labo (1956) studied 37 cases of the syndrome. They found

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that 84 per cent. had achlorhydria and sideropenia, while riboflavin deficiency, as shown by the riboflavin content of the urine, did not occur unless the dysphagia had been present for longer than one year, and that it was not always present even in cases with longstanding dysphagia. In 45 per cent. of their cases there was a low serum protein and evidence of hæmolysis, and it was suggested that this might be an hitherto unsuspected factor in the condition.

Discussion of Ætiology

Primary dysphagia seems an unlikely explanation of the condition because:

(1) No one has yet produced cases showing the hypopharyngeal changes of web or stricture formation before the development of blood and epithelial changes.

(2) The blood and epithelial changes do not occur in other types of dysphagia, e.g. a benign fibrous stricture caused by swallowing corrosives. (Sacrez's case might be an exception to this observation.)

Two such cases have been investigated and treated in the E.N.T. Department of the Manchester Royal Infirmary during the past two years. Both were females and had suffered from dysphagia for 20 years.

Mrs. E. K., aged 65 years, had two considerable fibrous strictures of the pharynx and a history of swallowing caustics when young. (See X-ray plate.) There was no evidence of anæmia, iron deficiency or any of the stigmata of the Paterson-Brown Kelly syndrome.

Mrs. M. N., aged 56 years, had severe syphilitic cicatrization of the laryngopharynx which narrowed the lumen to approximately the size of a lead pencil and her diet had been semi-solid for many years. In spite of this she was well covered and had no anæmia nor evidence of iron deficiency. There were none of the stigmata of the Paterson-Brown Kelly syndrome.

(3) The blood and epithelial changes in the mouth and nails frequently occur in iron deficient states without dysphagia.

(4) The sex incidence is similar to that of iron deficiency anæmia.

(5) Dilatation by itself improves many cases, but not so effectively as when combined with iron therapy.

Riboflavin deficiency, whilst present in some cases, is absent in others and is, therefore, unlikely to be the basic cause of the condition. The clinical features of the syndrome differ in several respects from those of a pure riboflavin deficiency, particularly in the absence of kerato-conjunctivitis, and in the colour of the tongue.

Meulengracht, Murphy and Jankelson have reported cases successfully treated with riboflavin, but there seems some doubt in all these papers as to whether or not iron was also administered. Jankelson's cases resembled pure riboflavin deficiency, rather than a true Paterson-Brown Kelly syndrome.

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Iron deficiency is considered the most important causative factor because:

(1) Most investigators have found a marked iron deficiency in these patients, either with or without an associated hypochromic anæmia.

(2) Iron deficiency can cause the changes in the nails and buccal mucosa without any dysphagia.

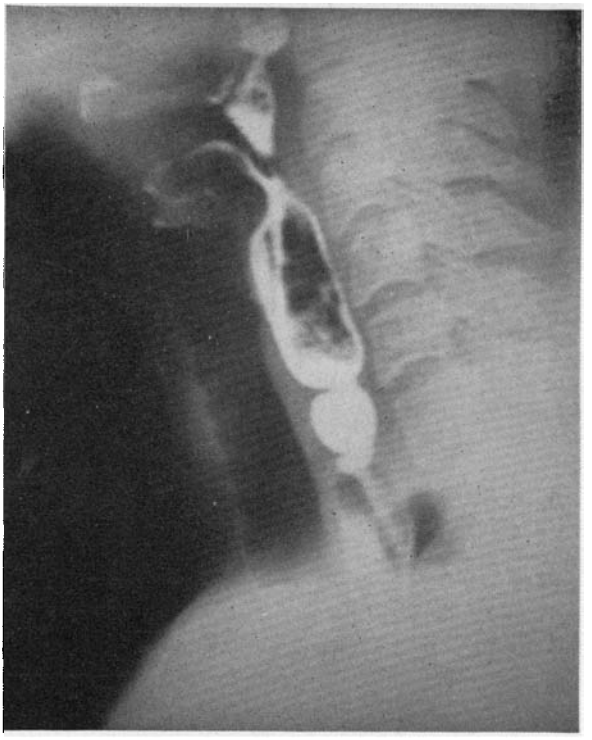


FIG. 1. Part 1.

(3) Iron therapy alone resolves the symptoms in many cases and has been shown to reverse the epithelial changes in the mouth, nails and probably the stomach also.

(4) The sex incidence of the Paterson-Brown Kelly syndrome is the same as that of iron deficiency anæmia.

(5) Experimental work with rats showed that iron deficiency can produce histological changes in the mucosa of the gullet similar to those seen in the Paterson-Brown Kelly syndrome, though no submucosal fibrosis developed.

Apart from these three major theories for the causation of the syndrome, various other factors have been emphasized by certain writers on the subject.

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Ahlbom (1936) and Wynder *et al.* (1957) have noted a high incidence of early edentia. Twenty-three per cent. of cases studied by Wynder *et al.*, had lost all their teeth before the age of thirty years.

Graham and Johnson (1932) and Sotgiu and Labo (1956) have noted changes in the blood suggesting a possible abnormality in the red cell fragility.

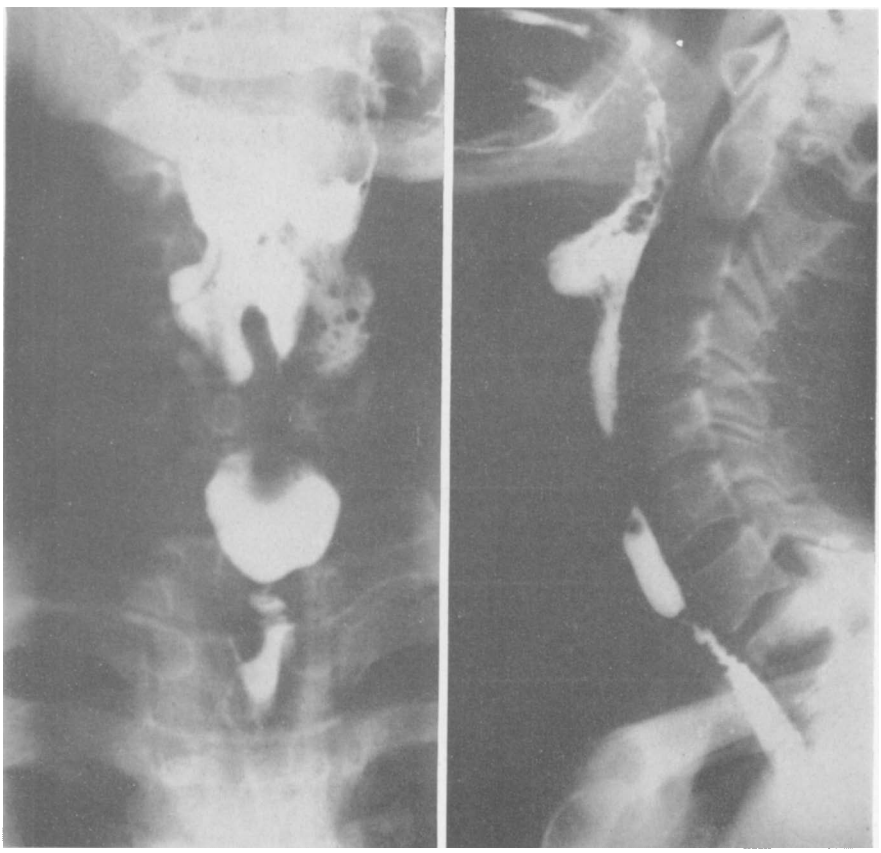


FIG. 2. Part 1.

Flusser *et al.* (1954) believe that sideropenia, ariboflavinosis, pellagra, sprue, the Paterson-Brown Kelly syndrome and Sjogren's syndrome are all related, there being a primary defect in the formation of co-ferments for tissue respiration ferments. The saliva may play an important rôle in the formation of apoferments of some of the B groups of vitamins. Cameron (1929) found the pH of the saliva within normal limits in his 25 cases.

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Histological Changes in the Hypopharynx

The histological changes have been reported by Suzman (1933), Savilahti (1946), Owen (1950) and Guichard *et al.* (1950) from post mortem material. McGee and Goodwin (1938) report post mortem findings in an atypical case. Except for this latter case, the writers found similar changes in the hypopharynx. These consisted of atrophy and thinning of the

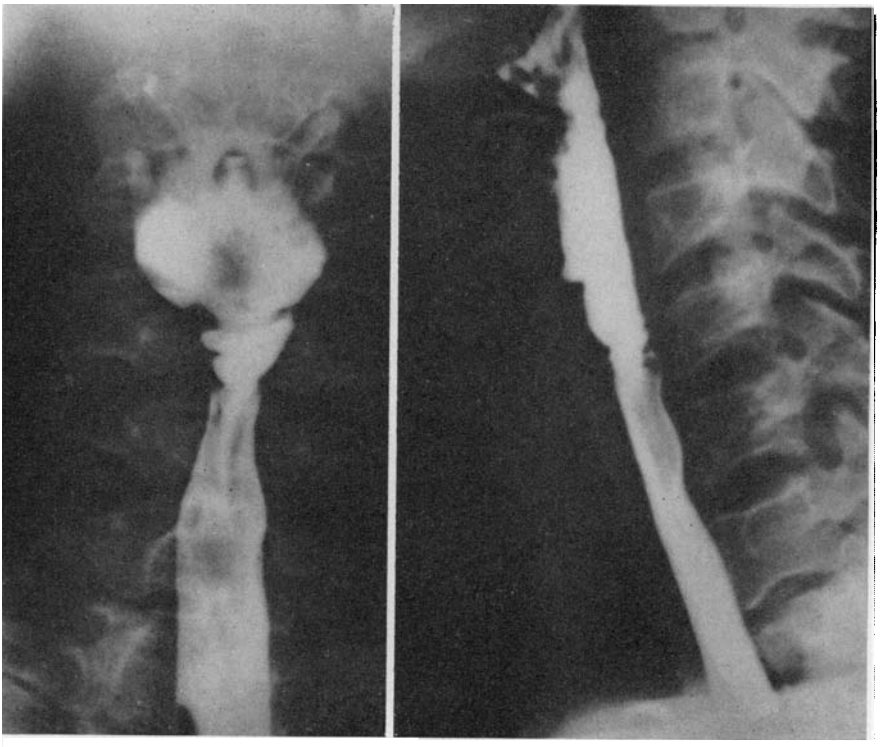


FIG. 3. Part 1.

epithelial layers with other areas of hyperkeratinization, while the submucosa was infiltrated with chronic inflammatory cells, especially where the overlying mucosa was much thinned. The appearance of the muscular layer varies from degenerative and atrophic changes to fibrosis.

Hoover (1935) shows a microphotograph of a biopsy through a web and this consists of a fibrous tissue core with a layer of mucosa on each side.

Reversibility of the Histological Changes

Successful iron therapy may reverse the nail changes as noted by Waldenstrom (1938). This also occurred in the case reported by Glazebrook (1944).

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Darby (1946) found that the macroscopic changes in the tongue recovered to normal with iron therapy, and Witts (1956) states that the lesions in the upper alimentary tract recover with satisfactory treatment, and recover completely in the case of the tongue. He also says that there may be permanent damage to the mechanism of swallowing.

Guichard *et al.* (1952) recorded the post mortem findings in a female patient of 83 years who, nine months before her death, had intensive oral and intravenous iron therapy for 3 months with relief of dysphagia, although her blood count and barium swallow appearances never changed. They found the following changes in the hypopharynx: (1) considerable desquamation of the epithelium; (2) atrophy of the mucosa and deep prolongation of the epithelial papillae; (3) atrophy of the submucosa with areas of chronic inflammation and vasodilatation and (4) œdema and some atrophic changes in the muscle layers. In this case, therefore, the intensive iron therapy, although relieving the dysphagia, had not reversed the histological changes.

Several authors report the result of investigations into the reversibility or otherwise of the changes in the gastric mucosa (Badenoch *et al.* (1957), Davidson, L. S. *et al.* (1938), Hallen (1938) and Leonard (1954). All found evidence of return of function in some of their cases after prolonged iron therapy. It was usually the young adults who responded satisfactorily. On the other hand, Lees and Rosenthal (1938) could find no return of gastric function in 21 cases after a year's iron therapy.

There is, therefore, some evidence that suitable treatment can reverse the histological changes in the gastric mucosa in young people, but it seems less likely that this can occur in older patients where the changes are more marked and well established. This was true of hypopharyngeal changes in the case reported by Guichard *et al.* (1952). The nail and buccal changes seem to be reversible with treatment in most cases.

The X-ray Changes in the Hypopharynx and Œsophagus in Paterson-Brown Kelly Syndrome

The typical X-ray changes and the best way for demonstrating these were described by Waldenstrom and Kjelborg (1939). A web, or rarely, multiple webs may be seen on barium swallow examination. The usual position is anteriorly in the post-cricoid region, but occasionally they occur lower down the cervical œsophagus (Videback (1944), Thornval (1948)). In very advanced cases, there may be a broader, cuff-like stricture below the web, caused by fibrous infiltration of the œsophageal wall. Such a condition is well illustrated by the following case.

Mrs. H. S., aged 46 years, attended the out-patients' department in March 1960 complaining of increasing dysphagia for 20 years so that her diet was now restricted to fluids only. She had taken iron intermittently over a long period

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of time. Her menses had always been very heavy. Her hæmoglobin when first seen was 60 per cent. and the serum iron 55 micrograms per 100 cc. She had marked glossitis, cheilosis and kiolonychia and her barium swallow showed the following result.

Treatment by intravenous iron improved her blood picture so that the hæmoglobin rose to 84 per cent. in 5 weeks. There was, however, no change in her swallowing. A radium menopause was performed in April 1960 and forcible dilatation of the stricture was carried out in May 1960. After the dilatation her swallowing and general condition rapidly improved. She put on two stone in weight in 4 months. When seen in September 1960 she was swallowing well, the tongue had nearly returned, to normal hæmoglobin 92 per cent. and serum iron 165 micrograms per 100 cc. The barium swallow showed a good lumen in the area of the previous stricture, but a small web was present, now more easily seen than in the previous film and situated just above the area of the stricture.

Holmgren (1943) and Lindvall (1953) agree that malignant change usually occurs just above the site of the web and suggest this may be due to irritation of food stasis at this point.

The Treatment of Paterson-Brown Kelly Syndrome

The treatment will depend on one's concept of the ætiology. As previously shown, the cause of the syndrome has been attributed to primary spasm or stricture of the hypopharynx, riboflavin deficiency and iron deficiency, and the respective treatments are, therefore, dilatation, riboflavin or iron therapy.

Vinson (1940) believes that hysterical spasm is the primary cause and treats his cases by reassurance and bouginage, the latter being performed for its psychological rather than its physical effects. He says iron is not essential, but can be given to correct the secondary anæmia, but the blood picture took a long time to return to normal in his cases and one-third of them relapsed. Some needed many dilatations.

Many workers (Bingham, *et al.* (1953), Bronner (1913), Flett *et al.* (1946), Jones, A. M., *et al.* (1948), Kelly (1919), Moersch, *et al.* (1926) and McKenzie (1918) have emphasized the importance of dilatation, considering this to be the most important single step in the treatment of the condition. This can be done slowly with graduated bougies, but is often achieved by rupturing the web by passage of the œsophagoscope.

Ellenberg and Pollack (1942) state that true ariboflavinosis should be cured by three weeks' treatment with 0·25-0·75 mgms. of riboflavin per kilogramme body weight. Murphy (1940), Jankelson (1940) and Meulengracht (1941) have all claimed successes with riboflavin therapy.

Paterson (1937), Waldenstrom (1939), Nowak (1951), Cahn (1952), Sotgiu (1956), and Witts (1956) believe that iron therapy is the essential part of the treatment. The dysphagia will respond to this treatment alone in many cases, though others may also require dilatation.

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Iron therapy, if it is to be effective, must be prolonged and, if necessary, maintained indefinitely (Cahn, 1952), and large doses of up to 15 grs. ferrous sulphate thrice daily are indicated in the first instance (Jasinski (1949), Mettier *et al.* (1929), Paterson (1937) and Witts (1931). These cases are liable to relapse if therapy is stopped, and the cause will often be continued blood loss, e.g. menorrhagia, so that it is essential to do everything possible to correct this or the iron therapy will be ineffective. The addition of ascorbic acid to the iron will aid its absorption. The iron stores may not be replenished even when the blood picture has returned to normal, so that therapy should be continued for some time beyond this point and perhaps reinforced by intravenous iron therapy (Davidson, W. M., 1952).

Many writers suggest that a combination of all three methods of treatment will be required in some cases, i.e. iron and riboflavin therapy and dilatation. The latter is necessary if submucosal fibrosis has occurred in the gullet to a degree that seriously hampers the swallowing of a normal bolus. A few cases will be resistent to all treatment, requiring repeated dilatation (Owen, 1950).

Several other methods of treatment have been suggested by various authors—(Ferrando Botet (1949), Howell *et al.* (1953), Sotgiu and Labo (1956), Szenes (1949), and Tafana (1959)).

Iddles (1954) records a case in whom the stenosis of the hypopharynx was so severe that dilatation via an endoscope was impossible. External exploration and myotomy of the cricopharyngeus down to the mucosa brought complete relief of symptoms.

The Relationship of the Paterson-Brown Kelly Syndrome to Postcricoid Carcinoma

The belief that such a relationship exists is based on the following points:

(1) Many cases of postcricoid carcinoma give a history of preceding Paterson-Brown Kelly syndrome.

(2) A follow-up of cases of the syndrome shows that a significant number develop malignant disease of the hypopharynx.

(3) The sex incidence of postcricoid carcinoma is similar to that of the syndrome and there is thus a reversal of the usual sex incidence for carcinoma of the upper alimentary tract as a whole, which is dominantly male, in the postcricoid region, where 50-80 per cent. of the cases in Sweden and the United Kingdom occur in females.

(4) The histological changes in the hypopharynx seen in some cases of Paterson-Brown Kelly syndrome have pre-cancerous characteristics.

(5) The biochemical changes in cell metabolism probably present in the Paterson-Brown Kelly syndrome have similarities to the biochemical changes in malignant disease.

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Early writers on the subject of the Paterson-Brown Kelly syndrome (Bronner (1913), Brown Kelly, (1919) and Paterson (1919)) mentioned the development of malignant disease of the hypopharynx in their patients, though Vinson (1922 and 1940) says it occurs only rarely and does not think the incidence significant.

Cameron in 1929 pointed out the similarity in the sex incidence of Paterson-Brown Kelly syndrome and postcricoid carcinoma.

It was Ahlbom in 1936 who emphasized the importance of preceding Paterson-Brown Kelly syndrome in the development of carcinoma of the upper alimentary tract in females in Sweden. He studied 150 such cases and found 70 per cent. gave a history of preceding Paterson-Brown Kelly syndrome, although he considered even mild preceding dysphagia as sufficient evidence for diagnosis of the syndrome.

More recently Wynder, Hultberg *et al.* (1957) also from the Radiumhummet, Stockholm, studied 472 cases of carcinoma of the upper alimentary tract in males and females. They considered many possible pre-disposing factors including syphilis, tuberculosis, nephritis, diabetes, surgery, diet and the Paterson-Brown Kelly syndrome. The latter was the only significant factor, there being a high incidence in all female cases of carcinoma of the upper alimentary tract in all sites, and also in male cases of carcinoma of the lower hypopharynx.

A similar retrospective study was carried out by Videbaek in Denmark (1944) on 235 cases of carcinoma of the upper alimentary tract in females. He found clear evidence of preceding Paterson-Brown Kelly syndrome in only 6 cases: the sex incidence of carcinoma of the pharynx in Denmark is female: male: 24: 76:—and in Sweden, female: male: 57: 63.

The relative sex incidence for different sites of carcinoma of the upper alimentary tract in various countries has been studied by Ahlbom (1936), Koszarowski (1947) and Gros (1954). They all agree that the incidence in females, particularly in the hypopharynx is much higher in Sweden than in Germany, Denmark, Switzerland, France and the U.S.A., and this is probably because the Paterson-Brown Kelly syndrome is common in Sweden. The female incidence of postcricoid carcinoma in this country is similar to that for hypopharyngeal carcinoma in Sweden. Thus Koszarowski states the female incidence of carcinoma in the postcricoid region in Sweden is 40 per cent., in Germany 22 per cent. and in the U.S.A. 20 per cent. The figures for carcinoma of the mesohypopharynx are—Sweden 57 per cent., U.S.A. 12 per cent. and Switzerland 9 per cent. The female incidence in this country for postcricoid carcinoma is even higher than that for cancer of the mesohypopharynx in Sweden, e.g. Christie Hospital, 1937-1958—females 85 per cent.

A follow up of many cases of the Paterson-Brown Kelly syndrome to determine the numbers who develop malignant disease has been carried out in this country by Simpson, R. (1939), Flett (1946) and Owen (1950 and

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1960—personal communication). Their results vary considerably. Simpson found that 10 out of 18 cases of the syndrome developed carcinomata somewhere in the upper alimentary tract—most of them within two years of being seen. Owen followed up 28 cases for 15 years and found 5 developed postcricoid carcinoma. More recently he followed up 35 cases for 10 years and found 3 suffered malignant change. Both these series were treated with dilatation and iron therapy. Flett reported 100 cases of the syndrome seen between 1935 and 1945, none of whom had developed any malignant disease in the upper alimentary tract. Most of these cases had been followed up for less than 5 years, and Owen (1950) later reported that Flett had changed his original opinion that the condition was not pre-cancerous. Charvat (1951) reports from Poland on 30 cases of the syndrome in whom 7 per cent. developed malignant neoplasms.

What, therefore, is the incidence of malignant disease in cases of Paterson-Brown Kelly syndrome? Wynder, Hultberg *et al.* (1957) agree with Lundholme that the figure is approximately 10 per cent. Owen believes it is 15-30 per cent. and Tarle (1957) says one-third. Simpson, R. found over 50 per cent. of his cases affected.

Bonorino-Udaondo (1950), writing from South America, did not think the syndrome was pre-cancerous and Waldenstrom (1938) was critical of the papers written up to that time which suggested that it was so.

Savilahti (1946) believed that the histological changes he had noted in the hypopharynx in a post mortem on a case of the syndrome could lead to neoplastic change.

Flusser *et al.* (1954) consider that the biochemical changes in the Paterson-Brown Kelly syndrome are due to lack of iron and riboflavin for the formation of co-ferments for tissue respiration ferments. They point out that an upset of tissue respiration is one of the basic biochemical changes in malignant growths.

Finally, Simpson, R. (1939), Videbaek (1944) and author (1957) have all pointed out that the mucosa of the whole upper alimentary tract may become "pre-cancerous" so that multiple primary malignant neoplasms of the area may occur in these patients, although the hypopharynx is the site most commonly affected by malignant change.

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