SIMPLE ACHLORHYDRIC ANAEMIA, PLUMMER-VINSON SYNDROME, AND CARCINOMA OF THE MOUTH, PHARYNX, AND OESOPHAGUS IN WOMEN

OBSERVATIONS AT RADIUMHEMMET, STOCKHOLM

BY

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Simple achlorhydric anaemia among women is a familiar and fairly common disease which in its main features was described by Faber in 1909 and again in 1913. Dysphagia in combination with anaemia in women was first observed by Plummer in 1914. In 1919 Kelly and Paterson further differentiated this syndrome in which anaemia and dysphagia are the most important features. The syndrome has been called "Plummer-Vinson's syndrome" or "dysphagia associated with anaemia," since Vinson in 1922 supplemented Plummer's observations. Peculiarly enough this disease is hardly known outside of Great Britain and the United States.

Among the British and American authors who have contributed to the knowledge of these diseases some have pointed out the close relationship between simple achlorhydric anaemia and Plummer-Vinson's syndrome, and a few, above all Davies and Witts, both in 1931, have expressed the opinion that they constitute two somewhat different forms of the same disease. Observations upon a large number of cases at Radiumhemmet, the radiotherapeutic clinic of the Stockholm Cancer Society, also point in this direction, as the present report shows.

There are clinical features common to both forms. The patients are almost always females, usually between 15 and 50 years of age. They often give a history of weakness and anaemia of many years' duration, the anaemia frequently observed for the first time at 18 to 20. They usually state that teeth were lost early in life, often as early as 20 or 30 years of age, and that fissures or "eczema" appeared periodically at the corners of the mouth. The patients are pale, and occasionally have a tinge of yellow in the complexion. They are quite thin, and almost always edentulous.

Among our own patients we have not infrequently found a shrinkage of the opening of the mouth, a sign which is usually not described in the literature. The lips are thin and the opening of the mouth is small and inelastic. These changes, together with the absence of the teeth, and perhaps a slight change in the elasticity or consistency of the skin of the face, give these patients a rather characteristic appearance and suggest the diagnosis. The changes in the lips are undoubtedly of the same nature as the atrophy of the mucous membrane which one usually finds in the mouth and pharynx in these patients. This atrophy is most clearly seen on the tongue, which in typical cases is completely smooth.

Although lacking in many cases, a very important sign for the establishment of the diagnosis is the so-called koilonychia, "spoon-shaped nails." Even if this almost pathognomonic deformity of the nails is lacking the patient may say that the nails have been soft and have often broken off. Examination of the blood shows a hypochromic anaemia of varying degree, which, as a rule, is quite moderate. In 20 to 30 per cent. of the cases a moderate enlargement of the spleen is found.

Differential Diagnosis

The differential diagnosis between achlorhydric anaemia and Plummer-Vinson's syndrome depends upon: (1) the occurrence of dysphagia only in the latter; and (2) constant achlorhydria in the former, whereas the Plummer-Vinson cases may in some instances have retained the

capacity to secrete hydrochloric acid (Cameron). I consider it debatable whether these differences are not in reality only apparent or artificial. A patient with all the signs of simple achlorhydric anaemia but without achlorhydria cannot be given that diagnosis because the achlorhydria is included in the definition, but if such a patient has dysphagia the diagnosis of Plummer-Vinson's syndrome is made unhesitatingly. If, instead, we regard all these cases as belonging to a single group, anaemia becomes the only constant sign, with the possible exception of an early loss of teeth. It is true that achlorhydria, together with other signs, is usually found, but in certain cases the secretion of acid is more or less preserved.

We have often observed that even patients who have had a rather marked degree of difficulty in swallowing for twenty or thirty years before admission have not spontaneously mentioned this fact to the examiner. They regarded their inability to take more than "small swallows" more as an individual peculiarity than as a disease symptom. The dysphagia is in many cases so slight that it requires a very careful questioning in order to establish its presence. It is possible that for this reason the history of dysphagia is occasionally overlooked, and the patient is thus counted among the group with simple achlorhydric anaemia instead of among the Plummer-Vinson group. We have been able to show that this has happened in several cases which have been previously treated at other hospitals. In our material, if the mildest degrees of dysphagia are included, we have found cause to assign most of the cases to the Plummer-Vinson group, whereas it is usually stated in the literature that the number of cases in the Plummer-Vinson group is considerably smaller than in the other group.

The cause of the dysphagia has been the subject of a lively discussion in the literature. The opinion most generally accepted at present is that the dysphagia undoubtedly depends upon an organic change in the pharyngeal and oesophageal mucous membrane of the same atrophic character as that observed in the mouth. A reflex spasm or, possibly in certain cases, atony of the pharyngeal musculature might also be considered as a contributory factor. The difficulty in swallowing is usually localized in the post-cricoid part of the hypopharynx and the upper end of the oesophagus.

Relation to Carcinomata of the Upper Portion of the Digestive Tract

Four or five years ago at Radiumhemmet we saw for the first time two women, about 50 years of age, who had had obvious symptoms of Plummer-Vinson's syndrome since 20 to 30 years of age. Both these patients have shown marked predisposition to mouth carcinoma: one of the patients has had five different carcinomata in the lip and oral cavity up to the present time; the other patient has had three carcinomata. Our attention was drawn by these two cases to simple achlorhydric anaemia and Plummer-Vinson's syndrome, and we began to search for these syndromes among the female patients at Radiumhemmet. We soon found that we could obtain considerable evidence of their occurrence in about one-half of all women with carcinoma of the mouth, and also in a great majority of women with carcinoma of the hypopharynx or upper portion of the oesophagus.

A review of the literature dealing with the aetiological and predisposing factors in mouth and pharyngeal carcinomata shows that simple achlorhydric anaemia and Plummer-Vinson's syndrome are not mentioned at all.*

* Wassink has found that many Dutch women with cancer of the upper end of the oesophagus and a few with cancer of the mouth present some characteristic clinical features. From his description it seems almost certain that it is a question of Plummer-Vinson's syndrome, which is not mentioned, however. (Wassink, W. F.: *Gen. Bladen*, 1933, xxi, 1, and *Nederl. Tijdschr. v. Geneesk.*, 1935, lxxix, 29.)

However, a few of the authors—as a rule British laryngologists and internists—who have studied Plummer-Vinson's syndrome, have recognized the risk of the development of hypopharyngeal carcinoma in these cases. Kelly, Paterson, and Turner have emphasized this risk, and Cameron has pointed out that women with Plummer-Vinson's syndrome often develop hypopharyngeal carcinoma in the region in which the changes in the mucous membranes are especially distinct. He assumed that the same aetiological factor in one case produced hypopharyngeal carcinoma and in the other case led to Plummer-Vinson's dysphagia. A few cases of post-cricoid carcinoma with a background of dysphagia of long duration are briefly mentioned in the literature, but Suzman has given a detailed account of a case with Plummer-Vinson's syndrome in which a carcinoma developed in the mesopharynx. Other than this, one finds only vague allusion to the fact that the syndrome in question may induce a precancerous condition in the hypopharynx; and Plummer-Vinson's syndrome has nowhere been mentioned in connexion with carcinoma of the mouth in women, except for a case report by McGibbon of a patient with Plummer-Vinson's syndrome showing precancerous changes and multiple early carcinomata in the mucous membrane of the mouth. In the voluminous literature on simple achlorhydric anaemia I have been unable to find any reference to the fact that this condition predisposes a patient to carcinoma.

Analysis of Cases

Since 1931 we have seen about two hundred and fifty women with squamous-celled carcinoma of the mouth, pharynx, and oesophagus. One hundred and fifty of these have been questioned and examined with reference to signs and symptoms suggesting simple achlorhydric anaemia or Plummer-Vinson's syndrome, and the findings have been positive in about 70 per cent. This means, therefore, that we have seen during the past five and a half years no fewer than one hundred women with carcinomata who have also had one or other of these syndromes. Of these eighty patients the majority—about seventy—have had dysphagia, although in many cases this symptom has been quite insignificant. Follow-up examinations are now being made with this syndrome in mind, and in the near future I hope to be able to give, in a more detailed publication, definite figures of its frequency.

Even at the present state of the investigation, however, it is clear that a relationship exists between simple achlorhydric anaemia and Plummer-Vinson's syndrome on the one hand, and squamous-celled carcinoma within the upper portion of the alimentary tract on the other. It is most probable that this relationship has its foundation in the atrophic changes in the mucous membrane which are associated with the anaemic conditions in question. I am inclined to believe that carcinoma develops gradually in this mucous membrane in somewhat the same manner as, for example, in the scarred skin after a burn, after lupus, or after irradiation. Suzman has observed epithelial changes of a precancerous type in the mouth and pharyngeal mucous membrane of a case of Plummer-Vinson's syndrome at necropsy.

The association of these syndromes is especially striking with respect to post-cricoid carcinoma. This form of tumour is typically a tumour of women. From the few small statistical surveys which have been published it appears that in most countries from 70 to 90 per cent. of these patients are women. This is all the more remarkable since, according to the statistics for mouth carcinoma and pharyngeal carcinoma in most countries, women make up only 5 to 25 per cent. of the patients affected. In our material about 90 per cent. of the patients with post-cricoid carcinoma are women, and

about 90 per cent. of these women have either Plummer-Vinson's syndrome or simple achlorhydric anaemia. I am convinced that, in other countries where women constitute the majority of these cases of carcinoma, the syndromes in question will also be found quite frequently.

Other Predisposing Factors

In our Swedish material about 40 per cent. of the cases of carcinoma of the mouth occur in women. This is quite an extraordinary proportion. I am inclined to see the reason for this in a larger incidence of Plummer-Vinson's syndrome and simple achlorhydric anaemia in Sweden than in most other countries. In many countries men make up the majority of these cases (not infrequently 90 to 95 per cent.), and this fact has been used to support the opinion that tobacco, alcohol, and syphilis play a large part in the development of mouth carcinomata. In Sweden, where mouth carcinomata appear among women and men in about equal proportions, alcohol and syphilis are relatively unimportant with respect to women. The peasant women smoke pipes in certain districts, however, and this cannot be denied a certain importance in the development of carcinoma in some cases, especially in lip carcinoma. Of our women patients with carcinoma of the lip about 50 per cent. are pipe smokers. In mouth carcinoma in general only about 15 per cent. of the women have used tobacco. However, since about half of these women with mouth carcinoma have had Plummer-Vinson's syndrome or simple achlorhydric anaemia, one cannot deny that this syndrome is considerably more important as a predisposing factor in women than other heretofore known factors.

Taylor has recently studied a large number of cases of mouth carcinoma in women from an aetiological viewpoint. He did not regard tobacco or syphilis as important, but considered that irritation by prostheses was the most important predisposing factor. The great majority of the female patients were in fact edentulous. I venture the opinion that the absence of teeth among Taylor's patients may in many cases have been in reality only one sign of a simple achlorhydric anaemia or a Plummer-Vinson syndrome. In any case, prostheses can hardly be blamed for the development of post-cricoid carcinoma occurring typically in women.

The distinct relationship which appears to exist so often in Sweden between simple achlorhydric anaemia and Plummer-Vinson's syndrome, and carcinoma in the mouth, pharynx, and oesophagus, may perhaps also be demonstrated in other countries, even if their significance may not be so great as among our own patients. This relationship must be considered as having great practical significance as well as theoretical interest.

Practical Significance

From a practical standpoint it is of great importance that these two anaemic conditions be diagnosed early, and that the women suffering from them receive effective treatment. This pertains not only to the treatment of the disease as such, but also to the attempt to forestall the development of carcinoma. The patients must therefore be followed up by repeated examinations and the treatment renewed when necessary. If the dysphagia becomes worse roentgen examination and possibly hypopharyngoscopy and oesophagoscopy should be performed. In this manner, if carcinoma appears in spite of the "prophylactic" treatment, it should be possible to make an early diagnosis. The outlook for obtaining good results with prophylactic treatment is rather favourable, since we have quite an effective remedy for simple achlorhydric anaemia and Plummer-Vinson's syndrome—namely, iron in large doses. All authors in this field are agreed upon its rapid and almost specific effect.

Iron Deficiency

Good therapeutic results, together with other facts, have caused many investigators to regard these anaemic conditions as deficiency diseases. It is thought that an insufficient supply of iron may be of primary aetiological significance. This deficiency in iron is caused partly by food poor in iron, partly by decreased absorption of iron from food because of digestive disturbances. Woman, owing to menstruation, pregnancy, and lactation, has a larger expenditure of iron than man, and there has been a desire to explain the appearance of the disease predominantly in the female sex on this basis. Davidson and his associates, who have recently examined the iron content of the food of the poor people in Aberdeen, found that the amount in their diet was as a rule insufficient. In a series of 3,000 individuals from this element of the population they observed that a large number were anaemic, but that all of the cases with anaemia occurred among the women. About half of all the women were anaemic, and these anaemic individuals were, as a rule, between 18 and 50 years of age. In Sweden the poorer element of the population exists on a diet which is undoubtedly poor in iron (a small amount of meat, very little fruit, and practically no green vegetables); and it is possible that the numerous cases of carcinoma in women in our material may be related to this fact. A certain amount of support for this opinion is obtained from the fact that in Radiumhemmet's material of comparable cases of carcinoma among the better situated classes only 20 per cent. is made up of women, and of these women only two cases have had any sign of Plummer-Vinson's syndrome.

These aetiological speculations are, of course, indefinite. We must acknowledge that we do not yet know the cause of these anaemic conditions. If their aetiology were completely clear and we had, moreover, a truly specific therapeutic agent at our disposal, we should be able to speak of an effective prophylaxis in women against hypopharyngeal carcinoma in particular, and also against carcinoma of the mouth.

Conclusion

The syndromes discussed should command the attention of cancer investigators when looked at from this viewpoint, as these syndromes undoubtedly constitute excellent examples of conditions which are precancerous. Their tendency to predispose to carcinoma must be greater than, for example, that of syphilis, for a far greater proportion of our patients with carcinoma of the mouth and pharynx have these syndromes than have syphilitics, even though the incidence of syphilis probably is many times greater in the general population.

It also appears to be of great theoretical interest that in many of these cases the foundation for a carcinoma appearing at 50 or 60 years of age is already laid during the years immediately following puberty, or perhaps even earlier.

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ACUTE INFECTIVE POLYNEURITIS* WITH A REPORT OF FIVE CASES

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Acute infective polyneuritis is a comparatively rare disease, appearing practically at any time, but mainly affecting young males between the ages of 20 and 40. It is by no means a new disease, for Viets¹ in his abstract records that Graves gave a clinical description of this disease in 1828, and Duménil in 1846 placed multiple neuritis as a definite entity.

The disease has been shown by Wilson² to be caused by a living virus, which was successfully transmitted from man to monkey and recovered in pure culture; but in many later cases such conclusive evidence has not been obtained. A toxin, however, is produced which seems to have a selective action on the lower motor neurones, causing a chromatolysis of the ganglion cells of both the anterior horns and posterior roots, when a rapid segmental spread may occur, either ascending or descending to involve the whole cord. The toxin reaches the cord by absorption from the peripheral end-plates of the motor and mixed nerves, which show a true neuritis with swelling and fragmentation of their axis cylinders.

Types of Cases

Collier³ describes the cases as falling into two types. The first is that of a four-limb peripheral neuritis associated with an external ophthalmoplegia, the malady being apyrexial and painless with a rapid onset. In some of the cases the ophthalmoplegia is severe and may be absolute so far as the external muscles are concerned, the internal muscles escaping, while the limb paralysis may be slight, only showing itself by a weakness of the extensors of the periphery with an absence of reflexes. In other cases the limb paralysis is severe while the ophthalmoplegia is slight. The second group of cases resemble those described by Gordon Holmes⁴ and Bradford, Bashford, and Wilson²; they have a slight pyrexia with a less rapid onset. They also show a four-limb polyneuritis, but accompanied by a facial paralysis and often a slight general bulbar weakness. Here again the limb paralysis is in some patients the dominating part of the picture, while in others the facial paralysis predominates.

A third group of cases, however, must be included which start as a lower-limb polyneuritis, spreading rapidly upwards to involve the trunk and finally the muscles of respiration. This group cannot be distinguished from what is known as Landry's paralysis, for there is little doubt that the two are due to a similar cause, and, as Grainger Stewart⁵ has stated, any distinction is artificial.

Motor and Sensory Symptoms

In all these groups the paralysed muscles are flaccid, but do not show much wasting, and the reflexes are sometimes surprisingly obtained when voluntary power is almost absent. The paralysis also need not be truly peripheral, and is often more proximal than distal, so that a patient may be seen to have some movements of his fingers and toes though unable to move arm or leg. Sensory symptoms are usually present, being described in the early stages as pain or numbness and tingling in

* Abstract of address to the Stratford Division of the British Medical Association, March, 1936.