phase of the choroidal arteritis could be observed ophthalmoscopically, and the appearances are described.

I am deeply indebted to Dr. A. J. Ballantyne for his most valuable help with the pathology of this case, and my thanks are due to Air Marshal Sir H. E. Whittingham, Director General of Medical Services, R.A.F., for permission to publish this report.

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OBSERVATIONS ON THE EFFECT OF RIBOFLAVIN ON THE ORAL LESION AND DYSPHAGIA, AND OF RIBOFLAVIN AND BREWER'S YEAST ON DARK ADAPTATION IN A CASE OF SO-CALLED PLUMMER-VINSON SYNDROME*

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THIS report concerns a male patient admitted with a Plummer-Vinson syndrome including dysphagia, angular stomatitis, glossitis, achlorhydria, koilonychia and hypochromic anaemia. The oral lesion and the dysphagia during the first part of observation responded to riboflavin. The finding of impaired dark adaptation (DA) later seemed to offer an opportunity for testing the possible effect of riboflavin and allied factors.

These observations are part of a larger study on dark adaptation undertaken in an attempt to use this method for detecting disturbances in general metabolism, and studying quantitatively their possible relation to dietary factors.

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Case Report

Male patient, aged 39 years, admitted to the Dietetic Wards of the Central Middlesex County Hospital on February 16, 1943. Family history irrelevant. Personal history: 17 years ago operation (gastro enterostomy) for duodenal ulcer. Since then practically free from dyspepsia except occasional slight epigastric pain soon after meals. For the last 4 years complaining of soreness of the tongue and cracks at the corners of the mouth, the latter never having healed up completely. The nails were brittle for the last 10 months. Difficulty in swallowing for the last 6 months with sensation of food stopping in upper part of gullet. Lately he has become dyspnoeic on exertion, feeling generally very weak, and the mouth has become so sore that he "could hardly eat."

On examination: Hyposthenic build, general condition reduced. Very pale and markedly anaemic; the skin of the face is sallow and slightly wrinkled. The tongue is smooth all over with a slight magenta hue. The angles of the mouth are macerated with deep transverse fissures. Marked koilonychia. Chest and heart showed nothing abnormal. Blood pressure 120/60. Liver and spleen not felt, no oedema, no neurological abnormalities. R.C.C.: 3·94 mill., Hb: 38 per cent., W.C.C.: 7750, differential count normal. Gastric secretion: no free HCl after histamine. Gastroscopy showed marked atrophy of the mucosa ("atrophic gastritis"). Clinical diagnosis: Hypochromic ("simple achlorhydric") anaemia with so-called Plummer-Vinson syndrome.

Observations

In the first period of treatment (February 20-25, 1943) the patient was given a daily injection of 5 mg. of riboflavin for five days and no iron. On the third day he reported a striking improvement in his oral condition which was complete on the fifth day when the soreness of the mouth and the dysphagia had almost gone, and corners of the mouth appeared practically healed. The patient saying that "after many weeks for the first time I am enjoying my food again." The haemoglobin at this time was 40 per cent. In the second period of treatment (February 25-March 13, 1943) he was given daily: fersolate gr. 9, brewer's yeast 4 drachms, 150 mg. of ascorbic acid, and 6 more injections 5 mg. each of riboflavin. When discharged on March 13, 1943, his Hb was 61 per cent. and he was in good general condition. He was instructed to continue with daily 9 gr. of fersolate (Glaxo), 150 mg. of ascorbic acid, 12 gr. 5 tablets of Aluzyme and dilute HCl with meals, which he did for two weeks (March 13-27, 1943). On April 5, 1943, his Hb was 85 per cent. and remained the same until September 27, 1943, when seen again as an out-patient. He

was well except for a recurrence of the soreness of the corners of the mouth and slight dysphagia, but fingernails were now found to be of normal shape. Enquiry elicited the fact that he was complaining of burning sensations of the eyes, and that his vision in the dark was poor.

Mr. A. Rugg-Gunn, my colleague at the Central Middlesex County Hospital, also examined the patient on several occasions. He reported: Visual acuity, fundi and fields are all normal. Repeated examinations by the slit-lamp and corneal microscope showed a considerable increase in the vascularisation of the limbic zone, with slight encroachment into the clear area of the cornea, particularly in the lower limbus. The presence of concentric collateral vessels was noted here and there but was not a conspicuous feature. The remainder of the cornea was perfectly clear. Some observers have attributed changes of this character to riboflavin deficiency, but they are very often found in association with chronic irritation of many types, and the failure in this case to respond to treatment confirms the view that they are not necessarily characteristic of riboflavin deficiency. Throughout the whole period that the patient was under observation no change in the corneal vascularity was noted, except on the last occasion, October 4, when, on the whole, the proportion of empty to full vessels appeared to be less. Whether this is a true observation or not, and if true, whether significant or otherwise, is at present impossible to decide.

His dark adaptation (DA) was found to be markedly impaired. A serial study over the following eight months was instituted.

Method: DA was measured with a modification of the Crookes' instrument (Haines, 1938), investigated and described by S. Yudkin (1941). The technique has been described in detail elsewhere (Pollak, 1943). Only rod adaptation was recorded, and its course was determined by taking the time required to recognise the test object the brightness of which was reduced in small steps.

The variations in DA observed during the first eight weeks, before any specific treatment was begun, are shown in Fig. 1, right hand side (empty symbols). The disturbance in DA is characterised by a delay in the " rod " phase and a high " final " threshold after 45 minutes in the dark. In Fig. 2 the variations in DA during the whole eight months period of observation are recorded by plotting the times required to reach various levels of sensitivity: (A) representing the time to reach a level corresponding to 1=5 log. units, (B) corresponding to 1=4·35 log units, and (C) corresponding to 1=4·0 log units. These figures were obtained from curves smoothed in a fashion as shown in Figs. 1 and 3.

During the period from March 27 to September 27, 1943, the patient had no treatment; from September 27 to November 8,

1943, he had some small doses of iron, and on November 8, 1943, his R.C.C. was 5·16 mill. and his Hb was 105 per cent. No iron was given thereafter. After 9 days treatment with riboflavin (December 6-13, 1943), totalling 65 mg. (7 injections 5 mg. each, the rest was given by mouth) there was a small but, compared with the variations recorded during the previous two months, significant improvement in the patient's performance as shown by two curves recorded on the same (77th) day (Figs. 1 and 2). This improvement was, however, not maintained, the patient having discontinued treatment owing to a cold. When seen a month later his adaptation had fallen back to the initial level. There was no further improvement after another 4 days treatment with daily 6 mg. riboflavin by mouth, and as the patient was still complaining of a " bad cold " he was left without treatment for 4 weeks. At that time (118th day; vide Fig. 2) his DA was at or rather slightly below the initial level. From then onward (January 24, 1944; 119th day) he was given daily 4 teaspoonfuls (approx. 20 gm.) of dried (non-autolysed) brewer's yeast (Aluzyme). After 6 weeks treatment improvement in his DA began and continued, and after 4 months treatment it was restored to normal. Curves showing the course of DA before and during treatment with yeast

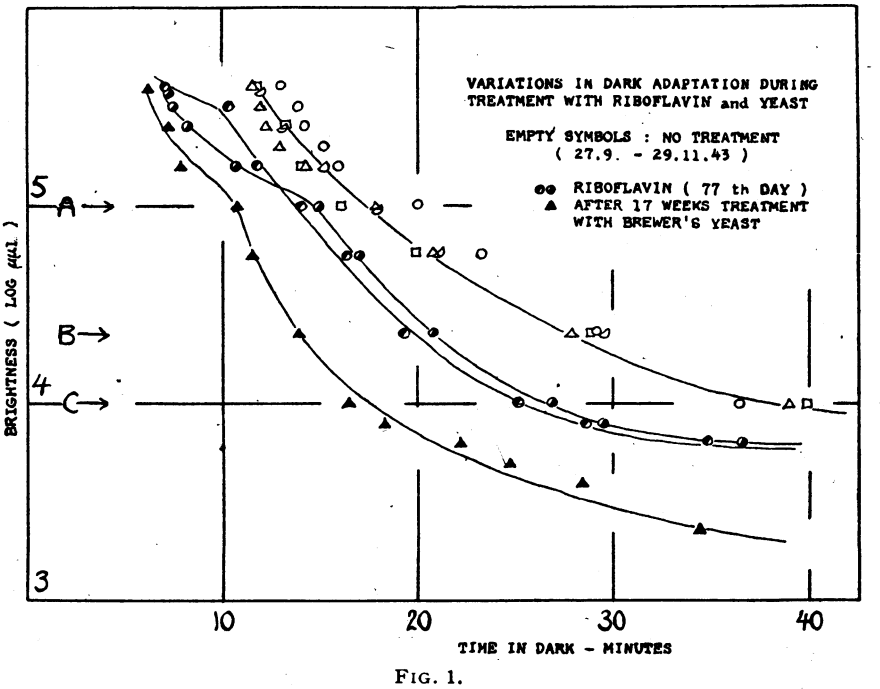

FIG. 1.

Variations in dark adaptation during treatment with riboflavin and yeast.

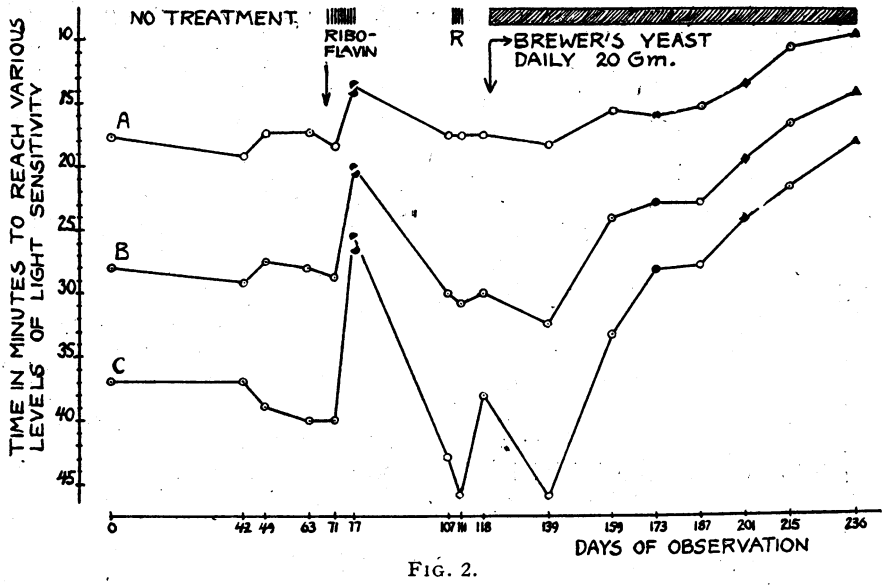

FIG. 2.

Variations in dark adaptation during eight months of observation recorded by plotting the times required to reach various levels of sensitivity, (A) corresponding to a level of 1=5·0 log units, (B) corresponding to 1=4·35 log units, and (C) corresponding to 1=4·0 log units.

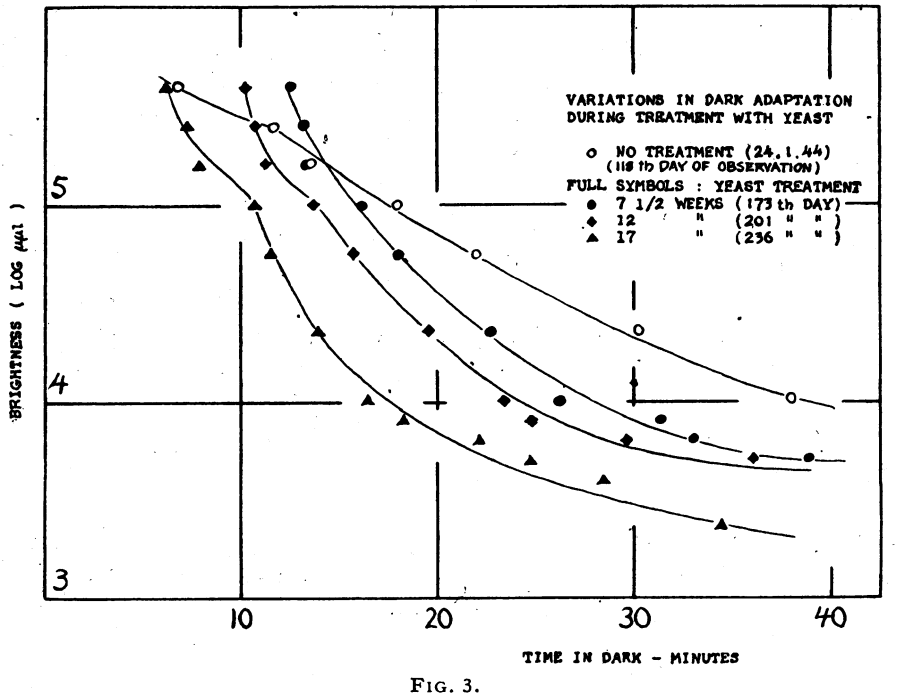

FIG. 3.

Variations in dark adaptation during treatment with yeast.

are shown separately in Fig. 3. Then, unfortunately, the patient was no longer available for further tests. Mr. Rugg-Gunn found no change in the slit-lamp appearance of the cornea on repeated examinations during the whole 8 months period. There was also no effect on the achlorhydria, while repeated gastroscopy was unfortunately not possible.

More emphasis may be laid on the considerable changes in DA observed during treatment with yeast than on the small, though apparently significant effect coincident with the administration of riboflavin. If the latter is disregarded, it is seen that during the first 4 months of observation there was no indication of spontaneous improvement but, on the contrary, a slight downward tendency is apparent. It is highly suggestive, therefore, that the restoration of normal function occurring under prolonged treatment with yeast was induced by the latter. An equally slow response to yeast has been observed in two more cases, one of which has been reported elsewhere (Pollak, 1943).

Discussion

The investigation reported here was undertaken with two objects in mind: First, a clinical one, to use DA in an attempt to detect disturbances in general metabolism, and the quantitative study of their possible relation to dietary factors; second, to provide further evidence in support of earlier findings (Pollak, 1943) concerning the influence of factors of the vitamin B complex on DA. To test the latter, two ways seem open: (*a*) to study patients with a " primary " deficiency (which, it is generally agreed, is at the present time rare in this country); (*b*) to select cases with a " conditioned " deficiency, *i.e.*, with metabolic disorders presumably reversible by the dietary factors in question.

Before dealing with the ophthalmological side of the present case some comment on the metabolic-nutritional background of the Plummer-Vinson syndrome will be necessary.

The epithelial changes occurring in the so-called Plummer-Vinson syndrome which may include dysphagia, glossitis, angular stomatitis with maceration of the corners of the mouth, achlorhydria and koilonychia, classically associated with hypochromic anaemia, respond to adequate treatment with iron though recovery may be slow and incomplete (Witts, 1931; Whitby and Britton, 1944). The concept that these changes are essentially due to iron deficiency has been widened by the observations of Waldenstrom and Hallén (1938) and Waldenstrom and Kjellberg (1939) who found that dysphagia, achlorhydria and koilonychia may occur without anaemia but associated with low serum iron levels and respond to treatment with iron (see Glazebrook, 1944). Waldenstrom and Kjellberg (1939) used, therefore, the term " sideropenic

dysphagia." A new approach to the pathology of these dystrophic changes of epithelial structures was suggested by the striking resemblance of the oral lesion in the "sideropenia" syndrome to the nutritional "angular stomatitis" (Stannus, 1912) (see *Brit. Med. Jl.*, 1940) which recently was recognised as a manifestation of a deficiency in riboflavin (Sebrell and Butler, 1938, 1939) and probably in other factors of the vitamin B complex.* The idea of such a deficiency being associated with (and possibly conditioned by) iron deficiency has received some support by observations on the curative effect of riboflavin on the angular stomatitis (Meulengracht and Bichel, 1941) and also on dysphagia and koilonychia (Lundh and Geill, 1942) in cases showing the so-called Plummer-Vinson syndrome. Although published evidence of this kind is scanty, this view appears to be widely accepted (Wintrobe, 1942; Bockus, 1943; Vanotti, 1944; Weder, 1944). It is argued that a deficiency in iron may condition disturbances in the metabolism of riboflavin and allied factors owing to the fact that cytochrome and cytochrome oxidase, which are haemin derivatives, are linked up in cellular oxidation processes with enzyme systems containing riboflavin and nicotinic acid, which probably also interact with other members of the vitamin B complex; the catalytic chain presumably most often breaking at the riboflavin link (*Brit. Med. Jl.*, 1940; Stannus, 1940, 1944; Vanotti, 1944; Pirie, 1943). Apart from such an interaction between the metabolism of iron and B vitamins, an important site of which may be the liver, there are obviously other interrelations, for example, in the intestinal tract, conceivable. Further, a lack of these factors in the diet, either pre-existing (Davidson and Fullerton, 1938), or resulting from lack of appetite and the oral and oesophageal condition, will have an aggravating effect. However, some attention should be given here to *intrinsic* disturbances underlying the changes attributed to iron deficiency as these may have a bearing on the disturbances in DA observed later. Witts (1931) has emphasised the importance of gastritis in the Plummer-Vinson syndrome; particularly the fact that the complete clinical syndrome as observed in the present case is hardly ever seen in the adult male except as a sequel to an operation on the stomach (Burger and Witts, 1934) points to post-operative changes as the underlying aetiological factor, such as atrophic gastritis and achlorhydria which were present in our case. As to the influence of gastric atrophy on general metabolism, the idea in favour of a direct endocrine-metabolic interaction between gastric mucosa and liver (Stannus, 1937; *Brit.*

* Some cases do not respond to riboflavin (or to riboflavin alone) but to nicotinic acid or pyridoxin, or apparently require the entire vitamin B complex in the form of yeast or liver extract (Smith and Martin, 1940; Machella, 1942-1943; Jeghers, 1943; Stannus, 1944).

Med. Jl., 1943) has received some more support recently by the demonstration of a lipotropic effect of whole stomach extract (Gillman, *et al.* 1944). In addition, changes in gastric secretion, in the motility and flora of the intestine, with resulting alterations in digestion and absorption of foodstuffs will have to be considered.

As in the present case the oral lesion and dysphagia had rapidly cleared up under treatment with riboflavin alone, it seems possible that a residual " subclinical " deficiency in this and allied factors (or, as I would prefer to put it, residual disturbances in metabolism underlying them) may have contributed to the impairment in DA found at a later date. (With this possibility in mind, and its relation to iron deficiency, the patient was not given large doses of iron but just enough to keep his haemoglobin at a normal level. No iron was given during the 6 months while the effect of vitamins on DA was studied.) In this respect perhaps also the history of a duodenal ulcer preceding gastro-enterostomy may not be entirely without significance, since impairment in DA has been found in ulcer subjects (Stewart, 1941; Pollak, 1943).

As to the changes in DA recorded here, the impairment of function in conjunction with the apparent response to treatment (particularly with yeast) may be taken as reflecting a disturbance in general metabolism which appears reversible by dietary factors of the vitamin B complex. From this a " relative deficiency " may be implied. In the same direction point recent clinical studies suggesting the existence of a nutritional factor not only in pernicious anaemia and in sprue but also in simple " atrophic gastritis " (for review see Rhoads, 1941, and Shapiro, *et al.* 1944) as indicated by regeneration of the gastric mucosa following treatment with choline (Shapiro, *et al.* 1944) and brewer's yeast (Abels, 1944). It is interesting to note, especially with regard to DA, that these agents are lipotropic, *i.e.*, they favourably influence hepatic metabolism, and further, that Abels *et al.* (1941) observed a rise in the plasma vitamin A levels in patients with gastrointestinal malignancy and peptic ulcer following treatment with choline and brewer's yeast, while vitamin A in large doses failed to produce this effect.

Since the Plummer-Vinson syndrome is believed to be a precancerous condition, the prophylactic significance in correcting the metabolic disturbances associated with it needs little emphasis; it is tempting to see in the latter, according to Rhoads (1942), one of the mechanisms underlying the cancerous degeneration of cells.

No attempt will be made here to speculate on the possible mechanisms by which riboflavin and yeast may influence DA, and it also seems impossible at present to express any definite views in terms of a photochemical or other mechanism.

Apart from our own tentative results reported here and elsewhere (Pollak, 1943) there seems to be no definite evidence in the literature concerning the effect of factors of the vitamin B complex on DA, though suggestions to this effect have appeared, but there is some scattered evidence that riboflavin and possibly allied factors may play a part in the visual process in general.

B vitamins in relation to vision (review of the literature).

B vitamins in relation to the visual process

v. Euler and Adler (1934) suggested that riboflavin (R) has a special function during twilight, changing short waves into light of a wave frequency for which the eye has maximum sensitivity, and Theorell (1935) believed that R. may have something to do with vision in general, and in particular with colour vision. Later Adler and v. Euler (1938) again suggested that " flavin . . . may take part in the visual process by means of its photochemical properties such as fluorescence and light sensitivity." The former is according to Pirie (1943) unlikely in mammals, but important considerations in favour of riboflavin forming part of the chromophoric group of visual purple have been put forward by Morton (1944) who has advanced a hypothesis linking up the " flavin " and " carotenoid " functions, vitamin A being concerned in the formation of visual purple by performing the reduction of riboflavin, itself undergoing oxidation to vitamin A aldehyde. That flavin is in some way concerned with the visual process seems suggested by Pock-Steen's report (1939) who described twilight blindness, *i.e.*, reduced visual acuity in weak daylight (twilight) and during inadequate artificial illumination, in patients with leiodystonia and sprue, which was not influenced by vitamin A but was cured by treatment with riboflavin. That the latter is essential to normal vision is also suggested by the well known work of Sydenstricker *et al.* (1940) who, being primarily interested in the corneal changes, observed disturbances of vision out of proportion to visible changes in the cornea in a group of patients, the majority being pellagrins, exhibiting oral, lingual and ocular signs of ariboflavinosis; with riboflavin visual acuity improved strikingly. While in these cases the influence of R. on the retinal or more central mechanisms of vision is admittedly compromised by possible corneal changes (Pirie, 1944), this factor seems less important in the cases reported by Fitzgerald Moore (1934, 1937, 1939, 1940) who described a pellagrinous syndrome in West Africa (Nigeria) associated with amblyopia due to retrobulbar neuritis; the patients recovered and visual acuity improved by treatment with yeast, fresh and autoclaved yeast extract (" Marmite ") and with riboflavin (1940). Although the involvement of a toxic factor, in the form of cyanogenic food, in these cases is still under discussion

(see Bicknell and Prescott, 1943), the conditioning effect of malnutrition (in B vitamins) in producing this form of amblyopia seems beyond doubt. Similar observations have also been reported by Verma (1942) and recently by Wilkinson and King (1944) from Hong-Kong who claimed curative effects on visual acuity with yeast, nicotine acid and R. Mention may be made here also of the study by Simonson *et al.* (1942) who found that addition of a mixture of B vitamins (daily 6 mg. B_1, 80 mg. nicotinamide, 0·24 to 0·32 mg. pyridoxin, 8 mg. riboflavin, and 80 to 120 J.-L. units of filtrate factor) to a normal diet of a group of healthy subjects produced an increase in the fusion frequency of flicker, the improvement beginning after three weeks treatment and reaching an optimum after 8 weeks. The relevancy of these observations lies in the possibility of a "nervous mechanism" participating in the visual process at low illumination (Lythgoe, 1940).

Concerning the effect of riboflavin on visual adaptation at low illumination (DA) only one paper, the preliminary report by Kimble and Gordon (1939) could be found. They reported that several subjects with both impaired DA as measured by the biophotometer and reduced blood vitamin A levels were restored to normal when R. was administered after vitamin A was found ineffective. These observations were taken as suggesting that riboflavin plays a part in the utilization of vitamin A (see Jeghers, 1942), but as yet no data seem to have been published by these or other workers substantiating this claim. We have observed (Pollak, 1943) significant improvement in DA in patients suffering from peptic ulcer during treatment with crude liver extract (Campolon) and brewer's yeast, the impairment in DA being attributed in the main to hepatic dysfunction, the working hypothesis being that a therapy believed to be favourable to hepatic metabolism might improve DA.

Summary

In a male patient admitted with a complete Plummer-Vinson syndrome the angular stomatitis and dysphagia cleared up rapidly by treatment with riboflavin. Half a year later, when the patient's blood picture was normal, a marked impairment in dark adaptation was found. The course of dark adaptation was followed up by serial tests with the Crookes's instrument over a period of 8 months. When the patient's performance had remained stationary for 2 months without treatment, a slight but significant improvement was recorded during treatment with riboflavin. After his dark adaptation had been allowed to fall back to the original level, the patient was treated with approximately 20 grams of brewer's yeast (Aluzyme) daily for 4 months; during this period his dark adaptation gradually returned to normal as shown by repeated tests.

A review is given of clinical evidence suggesting the association of a deficiency in riboflavin and allied factors of the vitamin B complex with the " iron deficiency syndrome," 'and the involvement of a " deficiency factor " in atrophic gastritis which is considered an aetiological factor in the present case.

This receives some support from the present study inasmuch as the impairment in dark adaptation in conjunction with the response to yeast may be taken as reflecting a disturbance in general metabolism which appears reversible by dietary factors of the vitamin B complex.

The observations recorded here and elsewhere suggest that dietary factors of the vitamin B complex may influence visual adaptation at low illumination under the experimental conditions herein described.

I wish to express my thanks to Mr. A. Rugg-Gunn for his help in the investigation and for reading the manuscript; to Messrs. Crookes' Laboratories for the loan of the adaptometer and to Messrs. Phillips Yeast Ltd. for their supply of aluzyme.

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SJÖGREN'S SYNDROME, ESPECIALLY ITS NON-OCULAR FEATURES*

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CHRONIC inflammatory changes in the parotid glands, usually without superadded abscess-formation but with recurrent exacerbations, leading to permanent changes in the glands in question —enlargement, sclerosis, atrophy, in irregular combination— is sometimes associated with similar changes in the other salivary glands, and more or less dryness of the mouth, also with similar chronic inflammatory changes in the lacrimal glands—though usually without obvious clinical enlargement—and with kerato-conjunctivitis sicca. Starting from the ocular side Henrik Sjögren

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