A post-mortem examination was made by Dr. L. C. D. Hermitte. Both suprarenal glands were atrophic, and histological examination showed simple atrophy, involving mainly the cortex (Fig. 3). The thymus was considerably larger than normal and the thyroid gland was also enlarged; the gonads and pituitary body were normal. The heart was small, and the lungs were slightly oedematous, the right lung having six lobes and the left lung four. There were no other important findings.

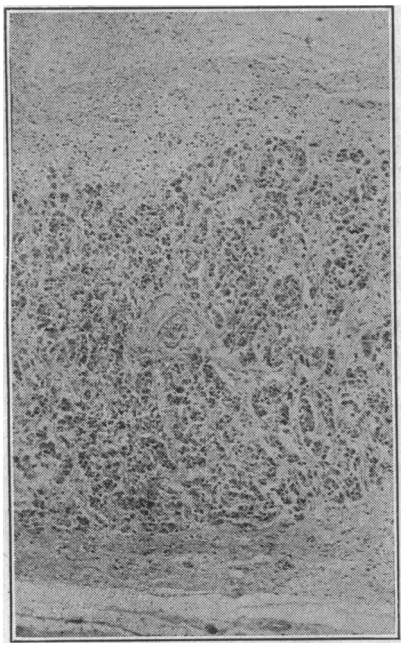

FIG. 3.—Case 2.—Section of suprarenal gland showing atrophy of the cortex with relative integrity of the medulla. Haematoxylin and eosin. (× 40.)

It is difficult to account for the sudden deterioration in this patient's condition and his failure to respond to treatment. It is possible that the maintenance of a normal blood pressure till the terminal stages of his illness was due to the relative integrity of the medullae of the suprarenal glands. The enlarged thymus gland directs attention to the possibility of myasthenia gravis, but there was not at any time clinical evidence of this disease. The congenital abnormality in the lungs is noteworthy.

### Discussion

Because these two cases of Addison's disease occurred in brothers, their family history was carefully and exhaustively investigated. Both parents were healthy, They came from a large city and their families were not in any way related. They had only the two children. The maternal grandparents died in old age and their children were not pigmented, though one son had a wasting disease in childhood but recovered and was lost at sea in the second world war. No relevant information was available regarding the paternal grandparents other than that the grandmother died at the age of 82 and that the grandfather is still alive and well, aged 79. There are several paternal cousins who have not been traced but who, at least until adult life, are known to have been healthy.

We are of the opinion that in each patient the disease was due primarily to atrophy of the suprarenal glands. It is not surprising that the younger brother had calcified abdominal glands, since he had been taking farm milk which was neither pasteurized nor boiled.

The occurrence of such a rare disease in two brothers and at an early age suggests the possibility that a genetic factor may be involved.

### Summary

The literature relating to the possibility of a familial factor in Addison's disease has been reviewed. The occurrence of Addison's disease in two brothers is described. In the patient who died, atrophic suprarenal glands and congenital abnormalities of the lungs were found at necropsy. The cause of the disease in the two cases presented is considered to be primary suprarenal atrophy. In view of the suggestive but inconclusive evidence afforded by this and other cases reported, we consider that the familial and genetic aspects of Addison's disease merit further study.

We wish to thank Professor E. J. Wayne for permission to publish these cases, and we are grateful to Dr. L. C. D. Hermitte for his report on the necropsy findings in Case 2.

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## THE FLUORESCENCE PHENOMENON OF THE TONGUE

BY

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When the mouth is viewed under ultra-violet light screened with Wood's glass a reddish-orange fluorescence is often visible on the dorsum of the tongue and sometimes on the teeth. This fluorescence has been recognized for some time, and has been proved to be due to the production of porphyrins by oral micro-organisms. So far, however, this fluorescence has not been adequately studied in relation to the various changes in the tongue that are known to result from nutritional deficiencies.

Several authors have described this phenomenon. Derrien (1924) noticed fluorescent points in dental cavities, which he attributed to decomposition of haemoglobin by bacteria. The fluorescence of the carious teeth or of tartar must be distinguished from that of healthy teeth in cases of congenital porphyria as first described by Mackey and Garrod (1925–6). Hymans van den Bergh (1928a, 1928b) described this fluorescence of the tongue in greater detail and endeavoured to explain its aetiology, but he did not study its clinical significance. More recently, Costello and Luttenberger (1944) attributed the absence of the normal fluorescence to vitamin-B deficiency. According to them it is intense in children but less marked in well-nourished adults.

Hagerman and Hirschfeld (1947) examined over 500 patients in a dermatological clinic. In about 60% of their patients the fluorescence extended over the whole tongue or covered about half of the dorsum, which was considered to be normal. About every fourth patient showed fluorescence over the whole surface. Tongues showing absent or very limited fluorescence were regarded as abnormal. These authors found that patients showing absent or greatly diminished fluorescence often suffered from the skin lesions usually associated with vitamin-B deficiency. They noticed also that vitamin-B preparations, especially those containing pantothenic acid, usually produced a change to the normal fluorescence (*British Medical Journal*, 1949).

Red fluorescence due to porphyrin is encountered in other parts of the human body, both in health and in disease. It has been seen in sebaceous comedones (Bommer, 1927, 1929) as bright-red points on the nose, around the lips, etc. Red fluorescence is often present in the menstrual and lochial discharges (Jones, Figge, and Hundley, 1944), probably due to porphyrin produced by bacterial decomposition of blood. It usually disappears a few days after menstruation. The tumour chloroma contains an excessively large amount of porphyrin (Thomas and Bigwood, 1935). Necrotic tumours (Policard, 1924) and many necrotic non-malignant tissues also exhibit red fluorescence.

## Method

Over 400 patients in medical wards and in the blood clinic of the Edinburgh Royal Infirmary were examined for fluorescence of the surface of the tongue and teeth. An ordinary ultra-violet lamp with Wood's glass was used.

Diseases characterized by changes in the tongue were specially selected, and, for comparison, examinations were also made in various other diseases and in a number of healthy people of different ages. In each case a rough sketch of the surface of the tongue was made. Besides ordinary data concerning age, sex, disease, etc., a short nutritional history was taken.

In some cases antibiotics, vitamins, and chemotherapeutic agents were given in order to investigate the influence of these substances on the fluorescence.

## Appearance of the Tongue under Ultra-violet Light

The majority of healthy persons show fluorescence on the posterior half or three-quarters of the tongue's surface. The rest of the surface, especially the anterior part, often has a greyish or whitish tinge. Only about 20% of healthy persons exhibit fluorescence on the whole tongue. The margins and the tip are as a rule free. The fluorescence has usually a red or orange hue, but it often has a pinkish or yellow tinge. Its intensity varies considerably in different persons.

Observed through a magnifying-glass, the fluorescence, which to the naked eye seems to be coalescent, is seen to be composed of small fluorescing points corresponding to the filiform papillae. The material scraped from such a tongue is composed of bacteria, epithelial cells, and particles of food, and on naked-eye observation under ultra-violet light shows a pinkish or red fluorescence.

Slightly coated tongues usually have a faint pinkish fluorescence. Intense red fluorescence is often associated with a thick coating. Tongues which do not exhibit red fluorescence have sometimes a quite normal appearance under ordinary light.

In a few persons small non-fluorescing lacunae are found on the red fluorescing area. These lacunae have a tendency to enlarge eccentrically in the course of time. In tongues with deep fissures, red fluorescence can sometimes be noted.

It is difficult to make an arbitrary distinction between normality and abnormality according to the extent of the area of fluorescence, as has been attempted by Hagerman and Hirschfeld. Our clinical material was divided simply into cases in which fluorescence was entirely absent and those in which it was present even to a very slight extent. The former were classified as negative, the latter as positive.

## Appearance in Healthy Individuals

For control purposes over 200 healthy persons of both sexes and various ages were examined. The examination of children was mainly carried out in the Princess Margaret Rose Orthopaedic Hospital, Edinburgh. Apart from their orthopaedic disabilities, the children were normal. Subjects over 60 years of age were selected mostly from inmates of Queensberry House for the Aged, Edinburgh.

The clinical material was divided into age groups. Of the total number examined, 59% were males and 41% females, but as sex seemed to exert no obvious influence on the incidence of the fluorescence phenomenon, males and females were considered jointly. Their nutritional history did not reveal any evidence of deficiency. The results are given in Table I, which shows that absence of fluorescence increases steadily with age.

TABLE I.—*Fluorescence in Healthy Individuals*

| Age Group | Total No. Examined | Fluorescence of Tongue | | % Without Fluorescence |
|---|---|---|---|---|
| | | + | − | |
| 0–20 years .. | 71 | 63 | 8 | 11 |
| 21–40 ,, .. | 50 | 44 | 6 | 12 |
| 41–60 ,, .. | 40 | 33 | 7 | 17 |
| 61–80 ,, .. | 38 | 28 | 10 | 26 |
| 81–100 ,, .. | 15 | 7 | 8 | 53 |
| Total .. | 214 | 175 | 39 | 18 |

In general, the intensity of the fluorescence in old people was definitely less than in children and younger adults. There were often slight atrophic changes in the filiform papillae in old people, but even in apparently normal-looking or coated tongues the fluorescence was often absent.

## Fluorescence in Certain Diseases

Special attention was paid to diseases which are associated with changes in the tongue.

*Pernicious Anaemia.*—Altogether 87 cases of pernicious anaemia were examined. Most of these were well-controlled cases that had been treated with liver, some of them for many years, or recently with vitamin $B_{12}$. Therefore, most of them had normal or nearly normal haemoglobin levels. Only six untreated cases were examined; all showed comparatively low haemoglobin levels. The results of the examinations are given in Table II.

TABLE II.—*Fluorescence of the Tongue in Cases of Pernicious Anaemia*

| Age | No. of Cases | No. Without Fluorescence |
|---|---|---|
| 21–40 years .. | 6 | 4 |
| 41–60 ,, .. | 34 | 18 |
| 61–80 ,, .. | 47 | 34 |
| Total .. | 87 | 56 (64%) |

Of the total number examined 64% were negative. The fluorescence in the positive cases was mostly faint. Compared according to age groups, the pernicious anaemia cases show a much higher incidence of negative cases than the normal persons. Cases with a completely atrophic smooth tongue were all negative, though some of them had haemoglobin values of over 100%.

It is not known whether any fluorescence was present before treatment in these cases. Examination of the six untreated cases, five of which were negative, throws some light on this problem. On treatment, the somewhat atrophic

tongues of four of them showed some growth of their short and atrophic papillae. After a few weeks the surface acquired a delicate whitish covering, and two of the patients previously entirely negative developed slight fluorescence. It seems, therefore, that liver therapy can in some cases restore the fluorescence; but treatment of patients with advanced atrophy of the tongue does not restore the filiform papillae or the fluorescence. The number of untreated cases was, however, too small for any dogmatic conclusions to be drawn.

*Hypochromic Iron-deficiency Anaemia.*—For comparison a group of patients suffering from iron-deficiency anaemia of different origin, but mostly nutritional, were examined. As is well known this type of anaemia is often associated with atrophic changes of the filiform papillae. It is also known that iron therapy frequently restores the condition to normal. Altogether 28 patients were examined—22 women and 6 men. Their ages varied from 28 to 70 years, the average being 46. Of the 28 examined 17 (60%) were negative. In general the positive cases in this group showed a stronger fluorescence than those in the group of cases suffering from pernicious anaemia. In one negative case, which was observed before and after treatment, restoration of papillae and faint fluorescence followed improvement in the haemoglobin level and in the general health, but in cases with permanently atrophic tongue the restoration of normal haemoglobin values did not produce any fluorescence.

*Sprue Syndrome.*—Fifteen patients suffering from the sprue syndrome, three being children with coeliac disease, were examined. The average age of this group was 33. The majority showed an atrophic tongue or had soreness of the tongue; they were all undergoing treatment. Eleven patients (73%) were negative. The four positive cases had been treated for several years with liver, folic acid, and other compounds of the vitamin-B group. In these four the tongue approached the normal in appearance and there was a slight fluorescence.

*Other Diseases.*—Small groups of patients suffering from other diseases were also examined. Gastro-intestinal diseases are often connected with lingual changes. Out of 22 cases of gastric and duodenal ulcer, with an average age of 43, nearly half showed absence of fluorescence. On the other hand cases of gastritis with heavily coated tongues usually showed an orange or a peculiarly yellow fluorescence. The results in a group of patients with an unusual appearance of the tongue are of some interest. Three cases with hairy tongue were negative. Seven cases with marked brown coloration of the coating of the tongue were all negative, and in two the fluorescence appeared after a few days' treatment with nicotinic acid. Twelve cases of so-called scrotal tongue (lingua scrotalis, lingua plicata), characterized by numerous deep furrows, were mainly negative. In a group of seven cases which showed signs of vitamin-B deficiency, particularly of ariboflavinosis, and characterized by angular stomatitis and red smooth tongues, fluorescence was absent. Groups of cases of diabetes, leukaemia, and other diseases did not give any conclusive results.

## Factors Influencing Fluorescence

Observations were made on patients treated for various reasons with antibiotics in order to study the effect of these drugs on the fluorescence of their tongues, which was positive in every case before the beginning of treatment. In addition, a number of healthy persons with strongly fluorescing tongues were selected for investigation of the local action of penicillin and other antibiotics on the fluorescence.

Penicillin was given in 500-unit lozenges (8–10 a day) to 5 persons. After a few days the fluorescence disappeared completely in each case, starting from the front and moving towards the back of the tongue. In three persons a brown colour of the tongue appeared with some soreness of the dorsum. With the cessation of penicillin treatment the red fluorescence reappeared gradually in a few days, starting from the back of the tongue. Penicillin given intramuscularly to four persons, 500,000 units daily for one week, did not abolish the red fluorescence.

Specially prepared streptomycin lozenges (50 mg. per lozenge) were given to three persons in a dosage of seven to eight lozenges a day for one week. In all three the fluorescence disappeared in four to five days.

In five patients treated with chloramphenicol (2 g. a day orally) for various diseases the fluorescence vanished rapidly, and at the same time the normal coating of the tongue disappeared. Glossitis and signs closely resembling ariboflavinosis developed in two of them.

Specially prepared chloramphenicol lozenges (5 mg. per lozenge) administered to three healthy persons in a dosage of 10 lozenges daily for a week brought about the disappearance of fluorescence in five to six days.

Similar results were obtained in three patients treated for various reasons with "aureomycin," 2 g. a day orally. Trials were also made with aureomycin lozenges (5 mg. per lozenge) on three healthy persons. It was found impossible to evaluate the local action of aureomycin on the fluorescence during treatment, as this substance itself produces a bright yellow fluorescence which covers the whole dorsum. However, with the cessation of the treatment the fluorescence, which had previously been strongly positive, remained negative for two to three weeks.

In contradistinction to the effect of the antibiotics, the use of sulphathiazole lozenges, six a day, seemed to have no effect on the fluorescence phenomenon.

Observations were also made on the effect of folic acid, riboflavin, and nicotinamide on five patients with signs suggestive of vitamin-B deficiency and with absence of fluorescence. In three of them, in whom definite regeneration of the papillae took place, a slight fluorescence developed.

As has been mentioned, reappearance of fluorescence was observed in some patients with pernicious anaemia after treatment with vitamin $B_{12}$, and the same phenomenon was noted in cases of sprue syndrome treated with folic acid, riboflavin, and nicotinic acid, and in cases of brown tongue treated with nicotinamide.

Pantothenic acid has some influence on the intensity of fluorescence. In healthy persons with faint fluorescence, treatment with pantothenic acid, 50 mg. three times daily for two weeks, produced a marked increase in its intensity.

## Discussion

There is no doubt that this fluorescence is due to the production of porphyrin by penicillin-sensitive micro-organisms. We do not know whether the porphyrin is synthesized by the bacteria or whether it is the product of decomposition of haemoglobin derived from food or from the host. Nor do we know the exact type of bacterium (or bacteria) concerned in porphyrin production in the mouth. Carrié (1934) expressed the opinion that the normal fluorescence of the tongue and of comedones is due to a particular Gram-positive bacillus. He claims to be able to cultivate this porphyrin-

producing bacillus in special media—Sabouraud and Fink media—but we have so far been unable to reproduce these results.

The actual role of porphyrin in the metabolism of the oral bacteria is also unknown. Pappenheimer (1947) suggests that porphyrin, at least in the diphtheria bacillus, might be produced in certain conditions in the process of synthesis of some respiratory enzyme, probably cytochrome b.

From the clinical point of view it is of interest to inquire why this porphyrin production is absent in certain normal and pathological conditions, and what is the part played by the vitamin-B group in its production. It seems that at least two factors are responsible for the fluorescence phenomenon: (1) the presence of porphyrin-producing bacteria; and (2) the presence of normal papillae, since a smooth tongue does not, as a rule, exhibit fluorescence. Judging from the fact that in a certain percentage of healthy and adequately nourished persons the normal-looking tongue does not show fluorescence, some other factors must also be responsible. We do not know why the percentage of negative cases in healthy persons increases with age.

It is doubtful whether the absence of fluorescence is of value as a clinical sign of vitamin-B deficiency, as has been suggested by certain authors. Some vitamin deficiencies, especially those of nicotinic acid, riboflavin, and aneurin, do produce lesions of the tongue and mucous membranes. In such cases where glossitis and atrophic papillae exist the absence of fluorescence is understandable. There is, however, no proof that reduced or absent fluorescence is always due to deficiency of the vitamin-B complex.

Factors such as vitamin $B_{12}$, folic acid, vitamin-B complex, and iron seem to have some influence on the restoration of fluorescence in certain conditions, doubtless due to their action in regenerating the papillae. In addition, the possibility that vitamins, as growth factors, have some action on the bacterial flora itself cannot be excluded. Mallinckrodt-Haupt (1938) reported a stimulating influence of vitamins, notably aneurin and riboflavin, on porphyrin production by bacteria *in vitro*.

The pathological states here investigated—pernicious anaemia, sprue syndrome, and iron-deficiency anaemia—are often associated with nutritional disturbances, and all are commonly characterized by lingual lesions. Brown (1949) and others brought about the disappearance of lingual lesions in pernicious anaemia and steatorrhoea by the administration of calcium pantothenate, inositol, nicotinic acid, folic acid, riboflavin, and liver extracts. Good therapeutic results were obtained in cases of glossitis in pernicious anaemia by treatment with pure vitamin $B_{12}$ (Stone and Spies, 1948; Schieve and Rundles, 1949)

There is no explanation why so many cases of pernicious anaemia, well controlled with liver and vitamin-B complex and showing an apparently normal tongue, still failed to exhibit fluorescence. Perhaps the porphyrin-producing organism was not present in the bacterial flora. Until this organism is identified the question cannot be properly answered.

Nothing definite can be said at present about whether the fluorescence phenomenon is only a clinical curiosity or whether it has some value as a guide to the state of nutrition in the individual. Nor is anything known about the significance and ultimate fate of the porphyrin produced in the mouth. It is reasonable to assume that at least some of it accompanies the digested food to the lower part of the alimentary tract.

In addition, the role of the normal bacterial flora in the mouth remains unexplained. We know very little about the function of bacteria in the digestive tract of man and their influence on the nutritional state of the individual. Recent experimental work has opened a new chapter in the role of bacteria in nutrition (Elvehjem, 1948; Johansson and Sarles, 1949). Lastly, an interesting hypothesis has been put forward by Frazer (1949) on the part played by the bacterial flora in the sprue syndrome and in pernicious anaemia. The importance of the intestinal bacterial flora in pernicious anaemia was stressed long ago by Davidson (1928). It is also known that a number of vitamins are synthesized in the intestinal tract, but, conversely, certain sulphonamides and antibiotics given orally may destroy the intestinal bacteria and change the microflora of the tract.

## Summary and Conclusions

The dorsum of the tongue often shows under Wood's light an orange-red fluorescence. This is probably due to synthesis of porphyrin by micro-organisms.

The tongue has been examined in over 400 persons. Fluorescence has been found in the majority of healthy individuals.

Absence of fluorescence becomes more frequent with increasing age; it was found in only 11% of children but in 53% of people over 80.

In certain diseases—pernicious anaemia, hypochromic anaemia, sprue syndrome, and vitamin-B deficiencies—there is a higher incidence of absent fluorescence.

The vitamin-B group and iron have some influence in the restoration of fluorescence. Antibiotics destroy fluorescence by their action on microflora.

The clinical significance of this phenomenon is not yet known. Its possible connexion with nutritional factors has been discussed.

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