- Davis, G. E., Cox, H. R., Parker, R. R., and Deyer, R. E. (1938). *Publ. Hlth. Rep.*, Wash., **53**, 2259.
- Derrick, E. H. (1937). *Med. J. Austral.*, **2**, 281.
- Durand, P. (1932). *Arch. Inst. Pasteur Tunis*, **20**, 395.
- and Balozet, L. (1940). *Ibid.*, **29**, 363.
- (1941). *Ibid.*, **30**, 1.
- and Giroud, P. (1940). *Ibid.*, **29**, 25.
- Eyer, H., and Grützner, L. (1939-40). *Z. Hyg. InfektKr.*, **122**, 589.
- Felix, A. (1930). *System of Bacteriology*, **7**, 413, Med. Res. Cncl., London.
- (1933a). *Trans. roy. Soc. trop. Med. Hyg.*, **26**, 365.
- (1933b). *Ibid.*, **27**, 147.
- (1935). *Ibid.*, **29**, 113.
- and Petrie, G. F. (1938). *J. Hyg., Camb.*, **38**, 673.
- and Pitt, R. M. (1934). *Lancet*, **2**, 186.
- and Rhodes, M. (1931). *J. Hyg., Camb.*, **31**, 225.
- Rainsford, S. G., and Stokes, E. J. (1941). *British Medical Journal*, **1**, 435.
- Findlay, G. M. (1941a). *Proc. roy. Soc. Med.*, **35**, 157.
- (1941b). *Lancet*, **2**, 659.
- Fleck, L. (1931). *Z. Immunforsch.*, **72**, 282.
- Fletcher, W., and Lesslar, J. E. (1925). *Bull. Inst. med. Res., Fed. Malay States*, No. 2.
- Friedberger, E., and van der Reis, V. (1919). *Münch. med. Wschr.*, **66**, 1075.
- Gear, J., and Davis, D. H. S. (1942). *Trans. roy. Soc. trop. Med. Hyg.*, **36**, 1.
- Gildemeister, E., and Haagen, E. (1940). *Dtsch. med. Wschr.*, **66**, 878.
- Hudson, N. P. (1940). *J. infect. Dis.*, **67**, 227.
- Liu, P. Y., Zia, S. H., and Wang, K. C. (1938). *Proc. Soc. exp. Biol., N.Y.*, **38**, 682.
- Maxcy, K. F., and Havens, L. C. (1923). *Amer. J. trop. Med.*, **3**, 495.
- Megaw, J. W. D. (1921). *Indian med. Gaz.*, **56**, 361.
- (1930). *Bull. Off. int. Hyg. publ.*, **22**, 1527.
- Monteiro, J. L. (1931). *C. r. Soc. Biol.*, **107**, 1161.
- Mosing, H. (1938). *Bull. Off. int. Hyg. publ.*, **30**, 1715.
- Otto, R., and Bickhardt, R. (1941). *Z. Hyg. InfektKr.*, **123**, 447.
- Parker, R. R. (1941). *Amer. J. trop. Med.*, **21**, 369.
- Pijper, A., and Dau, H. (1930). *Brit. J. exp. Path.*, **11**, 287.
- (1931). *Ibid.*, **12**, 123.
- (1932). *Ibid.*, **13**, 33.
- Piza, J., et al. (1931). *C. r. Soc. Biol.*, **106**, 1020.
- Raistrick, H., and Topley, W. W. C. (1934). *Brit. J. exp. Path.*, **15**, 113.
- Snyder, J. C., and Anderson, C. R. (1942). *Science*, **95**, 23.
- Steuer, W. (1942). *Z. Immunforsch.*, **101**, 102.
- Weigl, R. (1923). *Z. Hyg. InfektKr.*, **99**, 302.
- (1930). *Bull. Acad. polonaise des Sciences et des Lettres, Cracovie*, p. 25.
- Weil, E., and Felix, A. (1921). *Z. Immunforsch.*, **31**, 457.
- Weil, H. (1937). *Amer. J. publ. Hlth.*, **27**, Suppl. 141.
- White, P. B. (1933). *Brit. J. exp. Path.*, **14**, 145.
- Wohlrab, R. (1942). *Klin. Wschr.*, **21**, 455.
- Wyckoff, R. W. G., and Bohnel, E. (1942). *Proc. Soc. exp. Biol., N.Y.*, **40**, 712.
- Zinsser, H., and Castaneda, M. R. (1932). *J. exp. Med.*, **56**, 455.

CIRCUMCORNEAL INJECTION AS A SIGN OF RIBOFLAVIN DEFICIENCY IN MAN WITH AN ACCOUNT OF THREE CASES OF ARIBOFLAVINOSIS

BY

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From the heterogeneous collection of signs and symptoms called pellagra a number of specific syndromes are gradually becoming distinct. In 1938-9 Sebrell and Butler first described the specific syndrome of riboflavin deficiency in man, characterized by undue redness of the buccal mucous membrane at the angles of the mouth, by softening of the skin and subsequent fissuring at those angles, and by reddening, fissuring, and desquamation of the vermilion areas of the lips. Similar lesions were observed in the vestibule of the nose and involving the alae nasi and naso-labial folds; and seborrhoeic lesions of the nose, eyelids, and ears were frequent. These findings were confirmed by, among others, Sydenstricker, Geeslin, Templeton, and Weaver (1939), who drew attention to an associated dermatosis which was seen in 2 cases out of 6. A skin lesion, apparently similar, has since been noted by Duckworth (1942). In 1940 Kruse, Sydenstricker, Sebrell, and Cleckley added a further sign—viz., a specific glossitis, different from the red atrophic tongue of the pellagrin in that the organ is purple or magenta in colour, clean, with "flattened or mushroom-shaped" papillae and frequently fissured. They described for the first time ocular lesions characterized by circumcorneal injection, conjunctival congestion, and keratitis. Vascularization of the cornea followed by infiltrations and opacities had previously been described in ariboflavinosis in rats by Bessey

and Wolbach (1939). All the above stigmata have been repeatedly resolved by riboflavin but not by any other vitamin, and all except the dermatoses have been produced as the result of experimental feeding.

The ocular manifestations of ariboflavinosis were more fully described by Sydenstricker, Sebrell, Cleckley, and Kruse (1940), who found by means of slit-lamp examination of the cornea that a superficial vascularizing keratitis was the principal ocular manifestation of ariboflavinosis in man. Definite ocular changes could be observed in subjects presenting no evidence of cheilosis or glossitis. Photophobia, blepharospasm, dimness of vision, burning sensations in the eyeballs, "roughness" of the eyelids, and extreme visual fatigue were frequent symptoms, and impairment of visual acuity in the absence of any refractive error or opacity was also described. The earliest and most common ocular sign was found to be circumcorneal injection, which, though "often grossly visible," could always be discerned with the slit-lamp microscope, which revealed actual invasion of the cornea by capillaries in 37 out of 47 cases. Gross injection of the vessels of the fornix and sclera without evidence of infection was also common (43 out of 47 cases). Certain changes in the iris (frank iritis, congestion and pigmentation of the iris) were observed, but much less frequently. Many of these lesions resemble, but are actually distinct from, the ocular manifestations of avitaminosis-A.

Among the series of 47 cases described by Sydenstricker *et al.* (1940) was a group of 18 apparently well-nourished institutional employees, 14 of whom were between the ages of 20 and 35. Only 3 of them were taking "restricted" diets on account of intercurrent disease. All these subjects were considered to have circumcorneal injection, and in addition 13 showed evidence of corneal vascularization when examined with the slit-lamp. On account of this striking finding, but also because of the relative ease with which circumcorneal injection may be detected, it was thought worth while to determine the incidence of this sign in a series of individuals of the hospital class. The results of such an investigation are now presented because of their striking nature, because we believe that the experience of other workers will have been similar, and in order to draw attention to the care which is necessary before circumcorneal injection can be ascribed to ariboflavinosis.

Material and Methods

The investigation was undertaken on a series of 204 cases seen during the routine work of the medical out-patient department of the Edinburgh Royal Infirmary between Oct., 1941, and March, 1942—i.e., during the season when the highest incidence of deficiency disease might be expected to occur. The ages of the patients, none of whom suffered from any ocular infection, varied from 12 to 69. Each subject was

Chart showing incidence of circumcorneal injection, in reference to age, among 204 cases.

examined for circumcorneal injection according to the description given by Sydenstricker and his colleagues, but in no case was the slit-lamp used, and no detailed examination for other stigmata of vitamin deficiency disease was made except in 8 selected cases referred to later. The great majority of the patients suffered from chronic organic disease, but, so far as is

known, none was febrile when examined. Cases of frank vitamin deficiency disorder (2 cases of scurvy, 1 of frank ariboflavinosis, and 1 of pellagra with hypochromic anaemia) are not included in the analysis, but are referred to specifically below.

The riboflavin used in this investigation was "lactoflavin" Roche, supplies of which were made available by Roche Products Ltd. Particular care was taken to ensure that the material was protected from the light, strict instructions on this point being given to all patients.

Results

Out of 204 cases examined, 70 (34.3%) presented evidence of circumcorneal injection. On further analysis the physical sign was seen to be unevenly distributed through the series, occurring with relatively greater frequency in the older patients (see Chart). Among subjects aged 50 or over (63 cases) circumcorneal injection was found in 43 (68%). These striking findings might at first be taken to indicate that one-third of all the patients, and two-thirds of the patients over 50, manifested evidence of ariboflavinosis. This interpretation, even taking into account that the investigation was made during the winter

and early spring of the third year of war, seemed to us untenable and to require further consideration of the possibilities involved. Essentially these seem to be (a) that we have not interpreted the description of Sydenstricker and his co-workers correctly, or (b) that circumcorneal injection cannot always be taken as evidence of ariboflavinosis. It is possible also that we may have erred on both counts. It was accordingly felt that a more detailed examination of a small number of cases would be of value. This was undertaken from two points of view, as follows:

1. On the basis of their willingness to co-operate, 8 subjects were chosen from the above series for more complete investigation, the results of which are briefly set forth in Table I. None of these patients suffered from obvious disease of the alimentary tract, and all were taking a usual diet, apparently adequate for their caloric, protein, vitamin, and iron requirements. They were instructed to make no alterations in their way of living during the period of investigation. With the possible exception of Case 1, there was no obvious difference in the degree of circumcorneal injection during or after oral or parenteral riboflavin therapy. Two cases given brewer's yeast after treatment with riboflavin also failed to improve.

TABLE I.—Showing Results of Riboflavin Treatment of 8 Subjects with Bilateral Circumcorneal Injection

Case	Sex and Age	Diagnosis	Other Ocular Symptoms and Signs	Other Stigmata of Possible Deficiency Disease	Riboflavin Therapy	Dosage (mg.)	Result
1	M 53	Chr. bronchitis. Emphysema	"Itchy" eyes	Dry, atrophic, pigmented skin	Oral 6 mg. p.d. for 20 days	120	? Nil. "Eyes feel a little clearer"
2*	F 69	None made	Unequal and irregular pupils. Previous history of iritis	Bruises easily. Undue fatigue	Oral 12 mg. p.d. for 7 days, then I.M. 10 mg. p.d. for 6 days	144	Nil
3	M 48	Lumbar fibrositis	Nil	Nil	I.M. 2 x 10 mg. on first day, then oral 6 mg. p.d. for 14 days	104	Nil
4†	F 54	Colloid goitre. Auricular fibrillation	Eyes easily fatigued	Nil	Oral 6 mg. p.d. for 27 days	162	Nil
5	F 46	Obesity and glycosuria	? Allergic conjunctivitis in spring	Nil	Oral 3 mg. p.d. for 10 days, then 6 mg. p.d. for 10 days, then 12 mg. p.d. for 6 days	162	Nil
6	M 40	Chr. (left) pyelonephritis. Under urological investigation	Nil	Nil	Oral 6 mg. p.d. for 14 days; 4 I.M. injections 10 mg.	124	Nil
7	M 42	Pleurisy. Unresolved pneumonia	Nil	General debility	Oral 6 mg. p.d. for 14 days, then brewer's yeast 2 oz. p.d. for 14 days	84+	Nil
8	M 50	Chr. bronchitis. Emphysema	Rapidly progressive presbyopia. Marked arcus senilis	Nil	Oral 6 mg. p.d. for 14 days, then brewer's yeast 2 oz. p.d. for 10 days	84+	Nil

* Gave a previous history of aphthous stomatitis four years ago.

† This patient was taking digitalis during the latter part of the investigation.

The riboflavin content of brewer's yeast is given by Fixsen and Roscoe as 1.5 mg. per 100 g.

TABLE II.—Effect of Riboflavin Therapy in 8 Cases of Frank Vitamin Deficiency with Circumcorneal Injection

Case	Sex and Age	Diagnosis	Other Signs and Symptoms of B-complex Deficiency	Riboflavin Therapy	When Given	Dosage (mg.)	Result
9	M 71	Scurvy	Peripheral neuritis. Sore tongue. Dry scaly skin*	Oral 6 mg. p.d. for 22 days + 2 I.M. injections of 10 mg. each	After ascorbic acid 5.9 g. and thiamin 0.35 g.	150+	? Nil
10	M 61	Scurvy	Nil	Oral 6 mg. p.d. for 28 days, with brewer's yeast 20 g. p.d. for 14 days	With ascorbic acid 500 mg. p.d. for 7 days	162+	Nil
11	M 58	Scurvy	Peripheral neuritis. Aphthous stomatitis. Dry scaly skin. Cured by brewer's yeast	Oral 6 mg. p.d. for 14 days	After ascorbic acid 3.5 g. and hesperidin 9.6 g.	84	Improved
12	M 60	Scurvy	Paraesthesiae; numbness in both feet later? cured by thiamin	Oral 6 mg. p.d. for 14 days + I.M. injection of 10 mg.	After ascorbic acid 3.6 g. hesperidin 48 g.	94	Improved
13	F 48	Hypochromic microcytic anaemia	Bright-red painful tongue. Buccal ulceration. Rough pigmented skin elbows and wrists†	I.M. 5 mg. p.d. for 10 days	With FeSO ₄ 9 g. p.d. and ascorbic acid 200 mg. p.d.	50	Cured
14	M 40	Scurvy	Marked peripheral neuritis and oedema responding to thiamin. Stomatitis. Sore tongue	I.M. 5 mg. and 10 mg. on alternate days	After ascorbic acid 5.5 g. and thiamin 0.35 g.	50	Cured
15	M 60	Scurvy	Nil	I.M. 5 mg. p.d. for 7 days, then brewer's yeast 2 oz. p.d. for 26 days	After ascorbic acid 6 g.	35+	Nil
16	M 40	Pellagra	Diarrhoea. Stomatitis. Red, raw, atrophic tongue. Thick dry pigmented skin †	I.M. 10 mg. p.d. for 5 days, then 12 mg. p.d. orally for 14 days	After ascorbic acid 5 g. and nicotinic acid 4.2 g.	218	Cured

* Circumcorneal injection very marked. No evidence of infection. Photophobia and blepharospasm, "roughness" of the eyes and undue visual fatigue all improved by riboflavin. Other signs and symptoms resolved by brewer's yeast or nicotinic acid.

† All cured by nicotinic acid.

It is clear, therefore, that a form of circumcorneal injection exists which is not cured by riboflavin even in large doses. In 8 cases this was not found to be associated with other evidence of riboflavin deficiency or with other stigmata of deficiency disease. It cannot, therefore, be ascribed to ariboflavinosis. It may be observed in this connexion that Youmans (1941) has evidently observed a number of cases of angular stomatitis (cheilosis), indistinguishable from those due to riboflavin deficiency, which failed to respond to oral or parenteral riboflavin therapy. He considered that these cases were unlikely to be due to riboflavin deficiency.

2. A second group of 8 subjects, all of whom presented evidence of frank vitamin deficiency disease, were studied in order to determine (a) whether circumcorneal injection similar in appearance to that already noted could be detected, and (b) whether riboflavin could resolve the abnormality. Table II summarizes the results of this investigation. Circumcorneal injection could be detected in all these cases; we have, however, records of subjects suffering from frank vitamin deficiency disease, especially scurvy, who do not show this clinical sign. Six of the 8 cases presented in addition other evidence of deficiency of the B-complex vitamins: of these, 3 were cured and 2 definitely improved in respect of circumcorneal injection by riboflavin therapy, the other manifestations of B-complex deficiency afterwards yielding to thiamin, nicotinic acid, or brewer's yeast. One case with marked circumcorneal injection showed no improvement from riboflavin or brewer's yeast, although other stigmata of B-complex deficiency were resolved and there was considerable, and almost certainly genuine, symptomatic relief (see footnote to Table II). Two cases of scurvy without evidence of B-complex deficiency had circumcorneal injection but did not respond to riboflavin therapy or to brewer's yeast.

It is clear, from the study of these cases, (a) that circumcorneal injection, even when associated with frank vitamin deficiency disease, cannot always be resolved by riboflavin, and is therefore not necessarily a stigma of ariboflavinosis; and (b) that a form of circumcorneal injection exists which is resolved by riboflavin but which has been, in our experience, invariably associated with other stigmata of B-complex deficiency. This latter finding confirms in part the observations of Sydenstricker and his colleagues, but seems to point to the fact that circumcorneal injection (as interpreted by us) is not in itself evidence of ariboflavinosis. The physical sign requires to be supported by other evidence of deficiency of the B-complex vitamins, or possibly by examination of the cornea by slit-lamp microscopy—a procedure of which we have no experience.

Further confirmation of these findings and of the classical description of clinical ariboflavinosis by Sydenstricker *et al.* is provided by the following 3 cases of the fully developed deficiency syndrome.

Illustrative Cases

Case 17.—This patient, a woman aged 53, had complained of the symptoms of flatulent hyperchlorhydric dyspepsia with considerable epigastric pain for some three months, together with recent loss of weight and constipation. On investigation she was found to have a small, probably benign, ulcer on the lesser curvature of the stomach. She had been dieting herself for many years. When examined she had photophobia, "roughness" of the eyes, "itchiness" of the lids, and undue visual fatigue for which she had recently been bathing her eyes each evening. Mild blepharospasm, marked reddening of the ciliary margin, and circumcorneal injection were also present. She had aphthous stomatitis and a painful fissure at the right-hand angle of the lips. Her tongue, which was often sore, was pale, smooth, and atrophic. She had recently become a little breathless on exertion, and had a resting pulse rate of 100 a minute and a blood pressure of 110/68 with no evidence of cardiovascular disease. Recently lassitude, depression, and undue fatigue, with pains across the shoulders and down the right arm, had been additional features of the case. This patient's ocular signs and symptoms were rapidly resolved by riboflavin in doses of 12 mg. daily by mouth. Thereafter, regulation of the diet, with the administration of brewer's yeast in doses of 1/2 oz. four times a day, produced remarkable clinical improvement. Pain disappeared within 2 to 3 weeks. She had much more energy and was able to climb stairs without dyspnoea. The resting pulse rate fell to 70–80, and the blood pressure increased to 128/80. The aphthous stomatitis was much improved but not cured. Four weeks after stopping brewer's yeast, and while she was still taking what appeared by normal

standards to be an adequate diet, she developed circumcorneal injection, "roughness" of the eyes, and mild photophobia. These again responded to riboflavin treatment.

Case 18.—A woman aged 56; with steatorrhoea following multiple abdominal operations. She had had cheilosis intermittently for two years. On examination there was marked and multiple fissuring at both angles of the mouth, in the naso-labial folds, and at the lateral canthus of both eyes. She had a very painful aphthous stomatitis with dysphagia and a smooth, pale, tender tongue. Circumcorneal injection was present together with "roughness" of the eyes and impaired visual acuity. Oral administration of riboflavin, 6 mg. daily for 6 days, produced considerable improvement, and daily intramuscular injection of 5 mg. for 10 days completely cured the cheilosis, circumcorneal injection, and ocular symptoms. The aphthous stomatitis, and especially the sore tongue, were not resolved by riboflavin, but responded to nicotinic acid in daily doses of 200 mg. by mouth. All the symptoms returned within 14 days after discontinuing the therapy, even although the diet, by normal standards, was more than adequate in respect of vitamins of the B complex.

Case 19.—This patient, a man aged 69, had been treated intermittently for "pernicious anaemia" since 1916, and for the last 10 weeks had been having injections of liver extract (pernaemon) every 14 days. At the beginning of the present investigation the Hb was 12.2 g. per 100 c.cm. (88% Haldane), with R.B.C. 4,000,000 and C.I. 1.10. He had been complaining for some six months of debility, lassitude, undue fatigue, and vague pains across the shoulders, down the arms, and in the back of the neck. For several years, especially in the winter and early spring, he had had a scaly non-erythematous skin lesion on the calves of the legs, forearms, and back of the hands that was always intensely itchy. On examination a dry "branny" skin was found, with perifollicular keratitis in both upper arms, patchy pigmentation on the back of both hands, forehead, and face, and deformed, ribbed, and very brittle finger-nails. Circumcorneal injection was present, associated with "roughness" of the eyes, some photophobia, and a previous history of iritis, of which residual evidence remained. There was marked cheilosis at the angles of the mouth but none elsewhere. The appearance of the tongue was very striking, the organ being large, somewhat painful and tender, irregularly fissured with large flattened papillae, and magenta in colour. The characteristic purple hue of the tongue in ariboflavinosis can be appreciated best if the organ is inspected within the mouth, where its colour can be viewed against the background of the palate. The tongue of the typical pellagrin appears relatively small and rough, and is redder than the palatal mucous membrane. The tongue in ariboflavinosis appears relatively large and smooth. It is, however, deeply fissured and strikingly more purple than the mucous membrane of the palate and cheek.

After several examinations at weekly intervals, during which no significant alteration in the clinical picture occurred, riboflavin 6 mg. daily by mouth was given. After 30 mg. considerable clinical improvement was noted in respect of the ocular changes, cheilosis, glossitis, and dermatosis. In particular, circumcorneal injection was completely resolved. This improvement occurred in spite of the fact that the patient had been receiving every 14 days an injection of liver extract which probably contains some riboflavin. Further treatment by 2 oz. of brewer's yeast daily maintained the clinical improvement, and appeared, after two weeks' administration, to have had a favourable effect on the dermatosis. The perifollicular keratitis was not, however, improved. The patient was seen again 26 days after all therapy had been discontinued. His general health had improved considerably, but cheilosis, glossitis, and circumcorneal injection were again present.

Discussion

A striking feature of the clinical course of the above three cases has been the relatively rapid return, within 2 to 4 weeks after treatment had been stopped, of symptoms and signs (*viz.*, cheilosis, glossitis, circumcorneal injection, and ocular symptoms) which are evidently to be ascribed to riboflavin deficiency, since they are identical with those described by Sebrell and Butler and by Sydenstricker and his colleagues, and which, furthermore, have responded (in one case on two occasions) to treatment with riboflavin. In 18 out of the 47 cases referred to by Sydenstricker *et al.* (1940) relapse occurred shortly after riboflavin therapy had been discontinued. Apart from 15 apparently healthy individuals whose diets could not be regarded as deficient or unusual, the majority of their cases were taking a frankly deficient diet. Analysis of the diets taken by Cases 17, 18, and 19 of the present series reveals that Cases 17 and 18 were certainly receiving between 2 and 4 mg. of riboflavin a day—on at least 3 days a week in Case 17 and daily in Case 18. Case 19 took a diet which

could not be criticized on any ground, and in addition received 2 c.cm. of liver extract every other week.

A possible interpretation of these findings is that the riboflavin requirements of certain individuals are unusually great, as the result either of abnormal utilization or of defective absorption, or both. The idea that synergistic reactions in respect of other vitamins condition the absorption and utilization of riboflavin must be taken into account in evaluating this possibility. Although the results of the present investigation may be taken to indicate the existence of at least two types of circumcorneal injection, only one of which is resolved by riboflavin therapy, an alternative interpretation would appear to be that the development of circumcorneal injection is conditioned by a number of limiting factors, only one of which is a relative deficiency of riboflavin in the diet. In the latter connexion it is of interest to recall the findings of Albanese and Buschke (1942), who observed the clinical manifestations of ariboflavinosis in rats occurring as the result of a lack of tryptophan in their diet. A relationship between the metabolism of protein and another vitamin of the B complex is indicated by the work of Banerji (1941), who found that the presence of a large amount of protein in the diet of rats prevented the bradycardia and loss of weight usually associated with thiamin deficiency, and also that the growth rates of rats on various graded levels of vitamin B₁ were better in each case with excess of protein than without it.

Summary and Conclusions

In a series of 204 unselected out-patients between the ages of 12 and 69 circumcorneal injection was observed in 70 cases (34.3%). In 63 of those aged 50 or over circumcorneal injection was found in 43 (68%).

The observations of Sydenstricker *et al.* on the occurrence of circumcorneal injection in ariboflavinosis have been confirmed, but a form of the condition exists even in subjects presenting evidence of frank vitamin deficiency disease which cannot be attributed to a deficiency of riboflavin, as it is not resolved by administration of the vitamin. The latter finding no doubt accounts for the relatively high incidence of circumcorneal injection observed.

Although circumcorneal injection may be an early stigma of ariboflavinosis it cannot be considered such unless supported by other clinical findings—cheilosis, glossitis, dermatosis, and ocular symptoms—or by slit-lamp examination of the cornea (Sydenstricker *et al.*). The result of a therapeutic test, however, probably still remains the best criterion.

Three cases of ariboflavinosis are described, and it is suggested that certain subjects manifest a requirement for riboflavin which, for reasons unknown, is unusually large.

ADDENDUM.—Since completing this paper we have had the opportunity of discussing the matter with Dr. Sydenstricker, who has seen with us several cases of ariboflavinosis confirmed by slit-lamp microscopy. It is evident that the circumcorneal injection which forms the basis of this communication differs in no material way, on purely clinical examination, from that described by Sydenstricker in frank ariboflavinosis.

REFERENCES

- Albanese, A. A., and Buschke, W. (1942). *Science*, **95**, 584.
 Banerji, G. G. (1941). *Biochem. J.*, **35**, 1354.
 Bessey, O. A., and Wolbach, S. B. (1939). *J. exp. Med.*, **69**, 1.
 Duckworth, G. (1942). *British Medical Journal*, **1**, 582.
 Kruse, H. D., Sydenstricker, V. P., Sebrell, W. H., and Cleckley, H. M. (1940). *Publ. Hlth Rep.*, Wash., **55**, 157.
 Sebrell, W. H., and Butler, R. E. (1938). *Ibid.*, **53**, 2282.
 — (1939). *Ibid.*, **54**, 2121.
 Sydenstricker, V. P., Geeslin, L. E., Templeton, C. M., and Weaver, J. W. (1939). *J. Amer. med. Ass.*, **113**, 1697.
 — Sebrell, W. H., Cleckley, H. M., and Kruse, H. D. (1940). *Ibid.*, **114**, 2437.
 Youmans, J. B. (1941). *Nutritional Deficiencies*, p. 108, Philadelphia.

DOCTORS FROM OVER-SEAS: HOSPITALITY AT L.C.C. HOSPITALS

The London County Council is offering hospitality at its hospitals to Service doctors and nurses from the U.S.A., Canada, Australia, New Zealand, South Africa, etc. Details of the arrangements have been sent to the various authorities concerned. There may be, however, doctors and nurses who will not hear about it through official channels, and also there may be some from the countries mentioned who are serving with the British Forces. Any such who would like to visit L.C.C. hospitals or stay there during short leave should get into touch with the Medical Officer of Health, London County Council, County Hall, S.E.1 (telephone WATERloo 5000, extension 6425).

SULPHONAMIDES USED LOCALLY THEIR ABSORPTION FROM SEROUS CAVITIES AND WOUNDS IN MAN

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The sulphonamides are the most satisfactory of the drugs at present available for use in preventing the development of infection in contaminated wounds. There is evidence to show that they are more effective when used locally in the wound than when they are given by mouth or parenterally, owing to the greater concentration at the site of potential infection. The local effects of these compounds depend on their individual bacteriostatic powers and their physical properties. To be of benefit the selected drug or mixture of drugs should be present in the wound fluids in sufficient concentration and for long enough for the infection to be wiped out or for the normal tissue reactions to obtain control of the situation. The rate of absorption of sulphonamides from wounds is therefore of importance, and the present study was undertaken to investigate this problem. As the work was interrupted by the change of appointment of one of the authors the results presented are unfortunately incomplete.

Methods.—Observations were made on patients undergoing operations, many of which were abdominal. Before the peritoneum was closed the sulphonamide was introduced in measured quantities. Powders were sprinkled or dumped into the cavity out of a small container and spread with the finger. Solutions and suspensions were inserted through a catheter, around which the peritoneum had been almost closed; in this way little or none of the drug was lost. The subsequent absorption was followed by taking blood samples at 6, 24, and 48 hours and by measuring the excretion in the urine.

Results

The results in 25 cases are shown in the accompanying table. These include 8 cases observed by Prof. R. S. Pilcher. Nearly 60 other cases were observed clinically, but they have been omitted from this table as the records are incomplete in some particular or other. The first group consists of 11 patients who received 5 g. of sulphanilamide powder. This group comprised 6 abdominal operations, 3 thoracoplasties (2 on children), 1 nephrectomy, and 1 wound of the forearm. The blood and urine figures varied somewhat irregularly, without particular reference to the nature of the operation; for conciseness they are given as an average. Three other cases received 7.5 to 10 g. and a fourth case 15 g., and the concentrations in the blood and urine were somewhat higher. It is seen that when 5 to 10 g. of sulphanilamide is placed in the peritoneal cavity most of the urinary excretion occurs during the first two days. An effective blood concentration was maintained for 24 hours, the maximum reading (at 6 hours) corresponding in this series to about 0.5 to 1 mg. per 100 c.cm. for each gramme of sulphanilamide inserted.

Three patients received 5 to 7.5 g. of "hypoloid sulphanilamide L.S.F." intraperitoneally. This is a Burroughs Wellcome preparation consisting of 15% sulphanilamide in solution as sulphanilamide lactoside sodium formaldehyde sulphoxylate, and it is intended for intramuscular injection. As seen from the table, most of the urinary excretion occurs during the first twelve hours, and probably bacteriostatic activity in the peritoneum is too brief for the optimum results to be obtained.

In 2 cases a wound was packed with gauze and an oil-in-water emulsion, Preparation C, made by the British Drug Houses Ltd. (sulphanilamide 30, beeswax 0.7, cod-liver oil 49, oleic acid 3.6, sodium hydroxide 0.5, water to 100 parts—Fuller, Hawking, and Partridge, 1942). In animals it has been