

## FLICKER FUSION IN MULTIPLE SCLEROSIS

BY

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This paper is concerned with a study of thresholds of critical flicker fusion frequency (C.F.F.) of a light stimulus in patients suffering from multiple sclerosis. The capacity of normal human vision to appreciate the intermittency of rapidly repeated light stimuli is a function of great physiological interest, and it may be impaired by disease at many sites in the visual pathway.

Thus Parsons and Miller (1957) examined cases of multiple sclerosis on the hypothesis that general damage within the central nervous system might be responsible for depressing critical flicker fusion frequency. However, they found the C.F.F. so frequently impaired in their group that they were forced to conclude that retrobulbar neuritis must play a part in damaging its perceptual mechanism. They noted a correlation with pallor of the discs but did not observe cases during the course of retrobulbar neuritis. They suggested the potential value of C.F.F. estimation as a diagnostic test. These observations showed such a striking difference between cases of multiple sclerosis and controls that it appeared profitable to validate them for estimations made with different apparatus, and if possible to confirm their conclusion that depression of C.F.F. was related to the occurrence of retrobulbar neuritis. The relation between C.F.F. and visual acuity and the visual fields in multiple sclerosis is also of considerable interest.

Kurachi and Yonemura (1956) investigated four cases of retrobulbar neuritis and demonstrated the slower rate at which the flickering light was fused subjectively.

Most of the work on flicker fusion has been carried out by ophthalmologists but psychiatrists have also taken an interest in the subject in relation to its impairment in organic psychosis. Phillips (1933) and Riddell (1936) have studied the visual fields by means of flicker from the point of view of the neurosurgeon and this work made it clear that C.F.F. might be depressed by lesions far removed from the retina and

the optic nerves. Teuber, Battersby, and Bender (1960) have used the method extensively in their work on visual field defects consequent upon penetrating missile wounds of the brain. Their chief interest was in flicker perimetry and a full summary of their work is given in their monograph (Teuber *et al.*, 1960). Miles (1951) has also described methods of testing the visual field by flicker vision.

### Methods

The apparatus employed in this study resembles that devised by Mayer and Sherman (1938) who were probably the first to use a neon indicator lamp, which has the several advantages described by Miles (1950). The apparatus consisted of a beat frequency oscillator, which delivered up to 250 v peak to peak through blocking capacitors to a Mazda type B neon lamp (rating 200-260 v). The oscillator frequency control was continuously variable and covered the range 5-50 c/s with 270° rotation of the control knob. The output waveform was rectangular and was derived from a sine wave so that the on and off periods of each cycle were equal in duration.

The neon tube was mounted at the closed end of a black painted trapezoidal box so that its centre was 45 cm. from the eye. Two hinged metal shutters were used to block the vision in either eye. These shutters could be controlled from the outside of the box so that the testing of binocular and monocular performance could be accomplished without altering the position of the subject. The area of illumination within the bulb remained constant at 2 cm. width, providing a visual angle of close to 2.5° for the visual distance of 45 cm. Though intensity of illumination was not repeatedly measured, the voltage of the oscillator output was frequently checked. The area of the stimulus, according to Hylkema's (1942) figures, was considered adequate to give optimum fusion frequency in the central area and to 'bridge' any but large steep-edged central scotomata that might be present.

The subjects were tested after lying or sitting quietly for 20 minutes to eliminate any possible impairment of performance by physical exertion. The test was performed in a quiet room. The ascending and descending figures for C.F.F. in cycles per second were measured alternately, and our usual procedure was to make three to five 'runs' with binocular vision and to repeat the procedure with each eye alone. Each run consisted of first ensuring that the subject perceived flicker at a low rate,

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increasing the frequency until fusion occurred and then estimating the frequency at which flicker reappeared while the frequency was decreased. The mean of the ascending and descending values separately gave the figures for the range of each eye and these are shown in the visual field charts in Figs. 2-6. The mean of the ascending and descending values together give the figures used in the tables and in the statistical comparisons. The justification for taking a mean of ascending and descending figures is that a single lower normal figure must be defined if the test is to be diagnostically useful. We were aware that the figures for cases of multiple sclerosis and controls would overlap. Because of this, observations made on a single occasion could only be useful in diagnosis when the mean C.F.F. lay below all the control figures. The value of serial observations is referred to later in this paper. Other criteria or determinants as summarized by Landis (1954) were necessarily not determined for each subject because of the need to keep the test a simple one without the complication of multiple factors. However, our figures for C.F.F. in normal subjects fall on the linear portion of the curve relating C.F.F. to intensity illustrated by this author.

Two series of subjects were studied concurrently. The first series of known cases of multiple sclerosis was composed of individuals who were mostly in-patients of the Department of Neurology and totalled 60 cases. The other series of controls was composed of 28 patients with disorders of the nervous system and two healthy workers in the Department. The diagnoses of the in-patients in this series included epilepsy, cervical spondylosis, hysteria, migraine, headache (investigation), cerebral tumour, poliomyelitis, polymyositis, polycythaemia vera, cerebral vascular disease, diabetic neuropathy, closed

head injury, and lumbar disc lesion. They were unselected except for the deliberate exclusion of patients suffering from disease affecting vision. The ages of the individuals in the two groups were restricted to the range of 10 to 58 years inclusive. Both groups contained a number of subjects with normal acuity and a number with diminished acuity. In the controls the diminution was due to refractive error, in the multiple sclerosis group to refractive error or to the effects of the disease on the visual system. A proportion of the cases had standard visual fields plotted by one of us (A.F.T.) to confirm defects or scotomata suggested by the history or by the findings on clinical examination, and in general the visual acuity may be accepted as an approximate indication of the function of central vision. Examples of the relation between the visual field and abnormalities of C.F.F. are illustrated later in this paper.

**Results**

As many other workers have found (Landis, 1954), it has not been possible to determine accurately a single numerical end-point for appearance and fusion of the flicker on descending and ascending scales respectively. The mean of ascending and descending values are therefore used in Fig. 1. It is obvious that there is a notable tendency for the eyes of the patients with multiple sclerosis to have much lower values for C.F.F. than the controls. All the controls have mean values of 29 c/s or higher (mean 35.0 c/s, S.D. 3.4). There can be no doubt about the abnormality of C.F.F. in the eyes at the lower end of the range. It is, however, possible to compare the

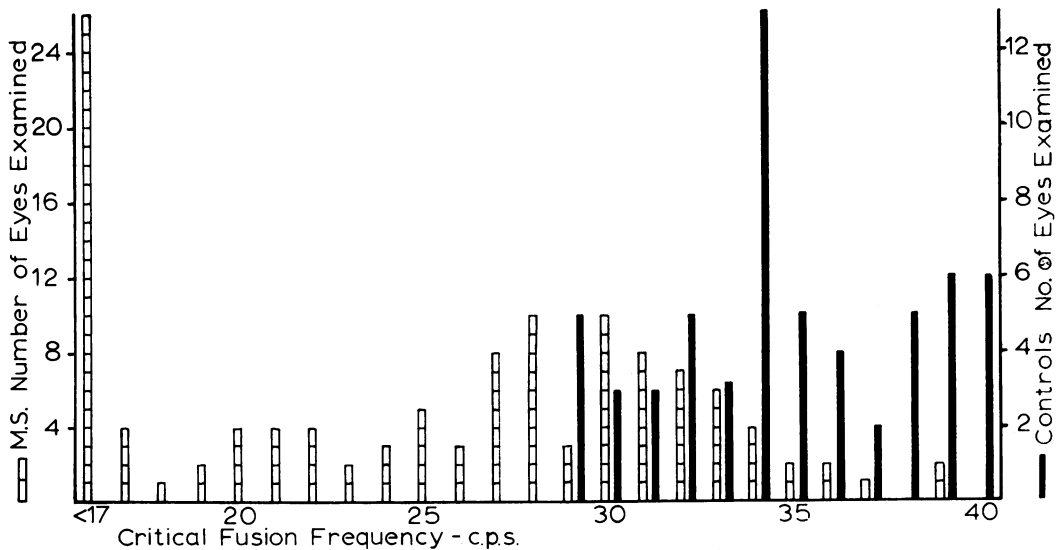


FIG. 1.—Mean figures for C.F.F. in individual eyes of 30 control subjects and 60 cases of multiple sclerosis expressed as the number of eyes showing C.F.F. in each category of whole numbers from 17 to 40 inclusive. The group showing C.F.F. of 16 c/s or less are bulked. Ascending and descending figures were averaged and category chosen as the nearest whole number below or equal to the mean value, i.e. 26.7 c/s is placed in category 26 c/s.

two groups statistically. With the assistance of Mr. D. Hewitt two comparisons were made. The first was between 22 control patients with normal visual acuity (6/6 or J1) in both eyes (mean 35.1 c/s, S.D. 3.35) and between 31 cases of multiple sclerosis with acuity of the same standard (mean 27.7 c/s). We considered this to be the most stringent comparison on the grounds that the selection of cases of multiple sclerosis with normal acuity would include those with least affection of the visual pathways. The values for individual eyes were averaged for each patient and the comparisons between the groups made by the  $\chi^2$  test. This showed a highly significant difference between the two groups ( $P < 10^{-4}$ ).

The second comparison between eight controls with diminished acuity in both eyes (mean 34.8 c/s, S.D. 3.3) and the cases of multiple sclerosis with normal acuity was also highly significant as would be expected from the small difference between the mean values in the two groups of controls.

**Relation between C.F.F. and Visual Acuity.**—The statistical comparison was made between cases of multiple sclerosis with normal acuity and the control group because it was evident from the figures that depression of visual acuity and C.F.F. were to some extent related.

TABLE I  
VISUAL ACUITY AND C.F.F. IN MULTIPLE SCLEROSIS CASES AND CONTROLS

C.F.F. (c/s)	Visual Acuity					
	59 Cases of Multiple Sclerosis			30 Control Subjects		
	6/6 + J1	< 6/6	Total	6/6 + J1	< 6/6	Total
24 and less	16	31	47	0	0	0
25-28	19	7	26	0	0	0
29 and over	36	9	45	47	13	60
Totals	71	47	118/118	47	13	60/60

Table I shows the relation between 59 cases of multiple sclerosis and 30 control subjects with normal and subnormal acuity in three categories of C.F.F., normal (29 c/s and over), reduced (25-28 c/s), and low (24 c/s and below). It should be noted that values for individual eyes are recorded in this table. The reason for considering values for single eyes is that in any one patient with multiple sclerosis the values for individual eyes may differ considerably, and it is therefore not possible to calculate a satisfactory mean figure for both eyes which could be used in comparisons with controls. This is in contrast to the statistical comparison described above where the problem was the differentiation between

the findings in individual cases of multiple sclerosis and control subjects. Table I shows that of the 47 multiple sclerotic eyes with C.F.F. depressed to 24 c/s or less, 16 (34%) had visual acuity of 6/6 or J1. In the group with moderate reduction to 25-28, 19 cases (73.1%) and seven cases (26.9%) had normal and reduced acuity respectively. These figures suggest that although there is a general relation between depression of C.F.F. and visual acuity the two tests of function are not closely linked.

**Relation between C.F.F. and Pallor of Optic Discs.**—A comparison between C.F.F. and the ophthalmoscopic appearance of the optic discs is shown in Table II.

TABLE II  
APPEARANCE OF OPTIC DISCS AND C.F.F. IN 60 CASES OF MULTIPLE SCLEROSIS

C.F.F. (c/s)	Appearance of Optic Discs		
	Pale	Normal	Total
24 and less	45	4	49
25-28	22	4	26
29 and over	26	19	45
Total	93	27	120/120

Table II shows the results obtained in the 60 cases of multiple sclerosis, the values for individual eyes being recorded, in two categories of disc colour (pale and normal) and in three categories of C.F.F. (29 c/s and over, 25-28 c/s, and 24 c/s and less). The discs were examined by us and a definite statement made that they were normally coloured or pale. Table II shows that in general normal discs were associated with higher values of C.F.F. and that pallor was associated with lower values. As the estimation of pallor is largely subjective no statistical evaluation was attempted; neither was any attempt made to grade the degree of pallor of the discs for the same reason. However, from these figures it appears that a pale disc indicates a chance of approximately 2.5:1 against the eye showing C.F.F. of more than 29 c/s. These figures also show that if the number of normal discs in each category of C.F.F. is expressed as a percentage of the total for the line, the proportion falls steeply with decrease in C.F.F. The percentage figures are 43, 15, and 8 in descending order of C.F.F. Furthermore, it will be seen that out of 120 examinations only 19 (15.8%) had normally coloured discs and C.F.F. in the normal range, 29 c/s and over. Although these figures include the subjective errors inherent in the estimation of disc pallor it is of interest to find so many of the cases of multiple sclerosis delineated from the control group by these criteria. Examination of the records for individual cases

shows that only five (8.3%) out of 60 cases had the combination of normal discs and normal C.F.F. of 29 c/s or over in both eyes.

**Critical Flicker Fusion and Retrobulbar Neuritis.**—The high incidence of depression of C.F.F. in multiple sclerosis and the association of this depression with disc pallor suggest that retrobulbar neuritis may be important in reducing critical flicker fusion. During the period covered by this study three of the cases of multiple sclerosis suffered an episode of retrobulbar neuritis. In one of these patients the C.F.F. fell from 34.5 c/s to 20 c/s, while the visual acuity was initially 6/6 and fell to 6/9. In the second patient C.F.F. fell from 28 c/s to 19.3 c/s and the acuity remained unchanged at 6/9. In the third patient, whose visual fields are illustrated in Figs. 2 and 3 (case R.W.), the C.F.F. was estimated eight days after the onset of retrobulbar neuritis and then two months later. During this period the C.F.F. rose from 17.5 c/s to 27 c/s, and the acuity from 6/9 to 6/5. These observations show a close relation between changes in C.F.F. and retrobulbar neuritis, the depression of C.F.F. in the third case becoming less with improvement in vision.

**History of Visual Disturbance and Critical Flicker Fusion.**—When the presence or absence of a history of an episode suggestive of retrobulbar neuritis in the multiple sclerosis group is tabulated against C.F.F. in three categories, 29 c/s and over, 25-28 c/s, and 24 c/s and below, there is a definite trend in the figures.

TABLE III  
PREVIOUS HISTORY OF RETROBULBAR NEURITIS AND C.F.F. IN 60 CASES OF MULTIPLE SCLEROSIS

C.F.F. (c/s)	History Suggestive of Retrobulbar Neuritis		
	Absent	Present	Totals
24 and less	9	17	26
25-28	7	10	17
29 and above	15	2	17
Totals	31	29	60/60

Table III shows this relation in 60 cases of multiple sclerosis. In this table the value of C.F.F. for the eye showing the lower average value is recorded. As the account of visual disturbance is based on the history from the patient it is not possible in many cases to define whether one or both eyes had been affected in the past; it was therefore impossible to compile the results for individual eyes with confidence in their reliability. The figures indicate approximately equal division of the patients without

a history of visual disorder into normal and abnormal categories of C.F.F. In contrast to these, only two patients, in whom a history of visual blurring or loss was obtained, have C.F.F. within the control range. If it is conceded that a history of visual impairment in these cases reflects the incidence of retrobulbar neuritis these figures provide further confirmation of the association with depression of C.F.F. In those cases where there is no history of visual loss, the reduced values of C.F.F., *i.e.*, 28 and below, found in 16 out of 31 cases suggests that there has been an episode or slow progression of retrobulbar neuritis in the past. In this connexion it is of interest that Gartner (1953), in a necropsy study, observed that the incidence of histological changes in the retina and optic nerves was higher than might have been expected from the history given by the patients during life. It is also possible that lesions in other sites may contribute to the depression of C.F.F. in these patients, as suggested by the findings on examination of the visual fields.

**Critical Flicker Fusion and Visual Fields.**—Five visual field charts are shown (Figs. 2-6) as examples of those encountered in this study. Figs. 2 and 3 show the fields in a patient aged 26 years (R.W.), eight and 44 days respectively, after an episode of retrobulbar neuritis affecting the right eye. Severe depression of C.F.F. (17.5 c/s) is matched by the paracentral field defect to test objects 2/2000 W and 6/2000 R. It will be noted that C.F.F. in the left eye (35.5 c/s), and for binocular vision (35 c/s), remain within normal limits. The visual acuity was only slightly depressed. Forty-four days later the right field has expanded and the C.F.F. has risen. However, it still remains outside the normal range, at a value of 27.5 c/s. The values for the left eye (37.5 c/s) and for binocular vision (35.5 c/s) are only slightly changed.

Fig. 4 (M.C.) suggests that central vision is important in determining C.F.F. These fields were recorded in a patient of 48 years and they show a right upper quadrant defect in both eyes. Central vision is intact and C.F.F. is only slightly below normal (28.5 c/s left, 28 c/s right).

Fig. 5 (C.D.) shows the fields in a 30-year-old man. There is a mild left upper quadrant defect in both eyes with preservation of C.F.F. within the normal range (31.5 c/s left, 35.5 c/s right). The fields in this case and case M.C. (Fig.4) suggest that small lesions in the optic tract may cause only limited disorder of the perceptual mechanism of C.F.F.

Fig. 6 is taken from a 26-year-old man. He had suffered several episodes of visual loss before the C.F.F. was estimated and had at one time had a lesion in the optic chiasm. Despite visual acuity of

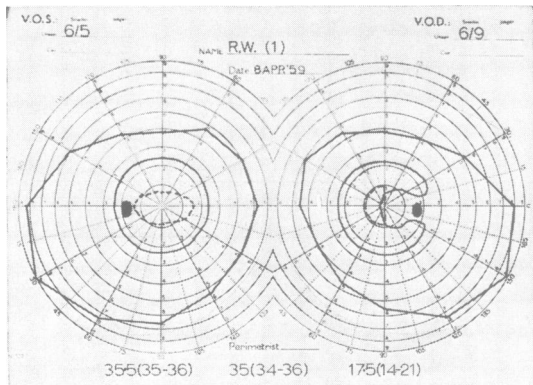


FIG. 2

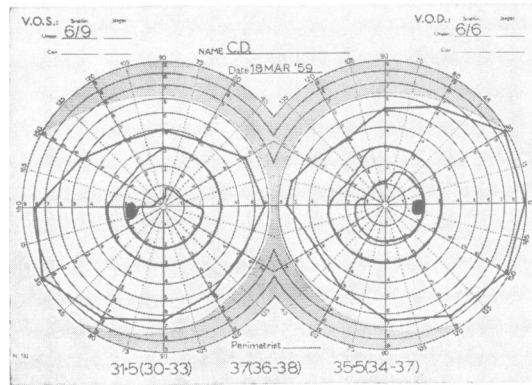


FIG. 5

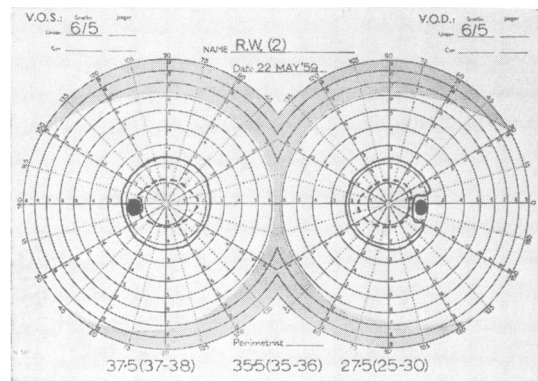


FIG. 3

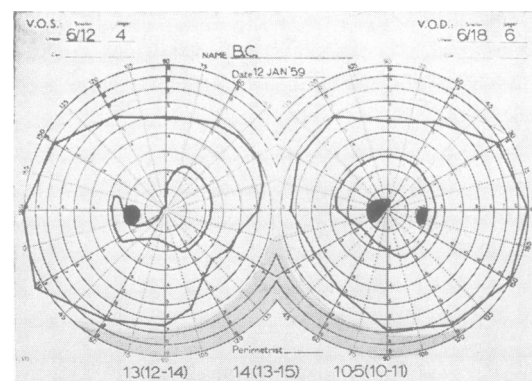


FIG. 6

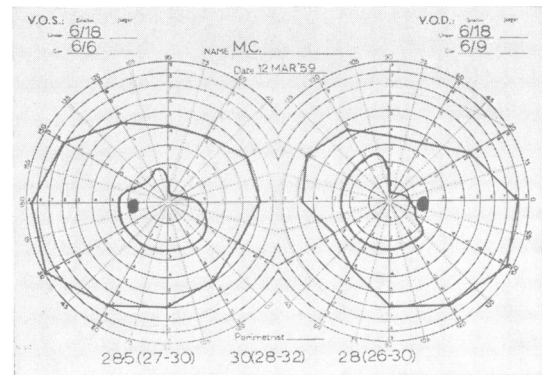


FIG. 4

FIG. 2.—Visual field of Case R.W. (1) eight days after onset of retrobulbar neuritis affecting the right eye. In this diagram and in Figs. 3-6 the outer solid line indicates the peripheral field to a test object 3/330 white. Inner solid lines indicate the field estimated on the Bjerrum screen with an object 2/2000 white. The interrupted lines indicate fields estimated with a test object 6/2000 red. The figures under each diagram give the mean C.F.F. (range in parentheses) and those placed centrally refer to binocular estimation of C.F.F.

FIG. 3.—Case R.W. (2). As in Fig. 1, 44 days after retrobulbar neuritis showing recovery of the visual field and of C.F.F. in the right eye.

FIG. 4.—Case M.C. to show minimal impairment of C.F.F. in relation to a mild right upper quadrant defect with little encroachment on central vision.

FIG. 5.—Case C.D. to show mild quadrantic defects with preservation of C.F.F. within the normal range.

FIG. 6.—Case B.C. showing severe deficit in central vision in both fields associated with impairment of both visual acuity and C.F.F. in a patient who had suffered severe retrobulbar neuritis in both eyes.

6/12 (right) and 6/9 (left) the depression of C.F.F. was very severe (10.5 c/s left, 13 c/s right).

(A more comprehensive study of the relation between C.F.F. and the visual fields is in preparation by one of us.)

### Discussion

There is no doubt that the groups of cases of multiple sclerosis and control subjects differ statistically to a highly significant degree. This applies particularly to those subjects with normal visual acuity. From the point of view of diagnosis it is important to set a lower limit to the normal range below which estimations may be considered abnormal with confidence. Fig. 1 showed that only five out of 60 control eyes had C.F.F. of 29 c/s, there being none below this level. Taking into account the standard deviation of our observations, we regard 28 c/s as being abnormal with fair certainty using this technique. We wish to emphasize that this applies only to estimations made with this design of apparatus and that values obtained with different light intensities and areas of illumination might well differ by many cycles per second. Indeed Landis (1954) warned, 'the fact that marked intra- and inter-individual variations do occur in C.F.F. measurement should serve as a cautionary warning to anyone working with any variety of C.F.F. phenomena'.

The estimation of C.F.F. with this technique is simple, provided that precautions are taken to maintain uniformity of the conditions of the test. It appears clear from this series that retrobulbar neuritis is the main cause of depression of C.F.F. in multiple sclerosis but factors such as the effects of exertion, body temperature and ambient temperature, intercurrent infections, and smoking have not been studied. All these are known to cause subjective visual disturbance in patients with multiple sclerosis and they might be expected to influence critical flicker fusion.

While the comparisons made in this investigation have been made between control subjects and patients in whom the diagnosis of multiple sclerosis had been made with certainty on clinical grounds, it is suggested that the estimation of C.F.F. may be

useful in displaying abnormality of visual function in patients with clinical symptoms and signs suggestive of multiple sclerosis but who give no definite history of retrobulbar neuritis.

The question of the relation between binocular and monocular values of C.F.F. is a complex one and requires further study. Both in controls and in cases of multiple sclerosis the binocular values are often slightly higher than the monocular values. Because depression of C.F.F. may be confined to one eye in the cases of multiple sclerosis and the chief interest of the study lay in the relation of C.F.F. to other tests of monocular vision, we have not considered the phenomenon of binocular improvement in this paper. It would also be of interest to measure the visual acuity by more accurate techniques (Walsh, 1957) and compare the results against C.F.F. findings.

### Summary

A simple means of testing flicker fusion frequency is described. Results in 30 control subjects and in 60 patients with multiple sclerosis are presented. They indicate that multiple sclerosis is often associated with depression of critical flicker fusion frequency in one or both eyes. The depression appears to be related to the occurrence of retrobulbar neuritis.

We wish to thank Dr. Ritchie Russell, Dr. C. W. M. Whitty, Dr. J. M. K. Spalding, and Dr. Honor Smith for permission to study cases under their care, and Mr. D. Hewitt, of the Department of Social Medicine, Oxford University, for his invaluable help with the statistical evaluation of the estimations.

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