The Flicker Fusion Frequency and Its Response to Nitroglycerin in Normal Subjects and in Patients with Cardiovascular Disease

By Ancel Keys, Ph.D., and Ernst Simonson, M.D.

Krasno and Ivy have claimed that the change after sublingual nitroglycerin in the frequency at which a flickering light appears to fuse (f.f.f.) sharply differentiates between cardiovascular normals and patients with coronary and/or hypertensive disease and that this test may be useful in detecting and evaluating such disease. On the basis of a detailed analysis of the original publication and of data on 304 men these claims are denied. Indications for further study of flicker phenomena are discussed and fiducial norms are presented.

The fusion (or critical) frequency of flicker is that rate of successive light flashes where the sensation of flicker disappears and becomes the same as that of continuous light. There is reason to believe that the fusion frequency of flicker (f.f.f.) in a subject with normal ocular structures depends on the time parameter of excitability of the visual pathways, primarily of the visual centers. While the literature on the flicker phenomenon goes back over a period of one hundred years, the application to physiologic or clinical stress situations is quite recent. Simonson and co-workers found a decrease of the fusion frequency of flicker in fatigue of the central nervous system and in various types of pathology, among others in a group of 21 patients with heart disease. This seemed to be in harmony with observations on the fatigability of cardiac patients in mental as well as in physical work, but no suggestions were made as to the potential value of this method for diagnosis or prognosis of cardiac disease.

Recently, Krasno and Ivy have reported studies on the fusion frequency of flicker before and after the sublingual administration of 0.4 mg. of nitroglycerin and stated, “We believe our results clearly show that the nitroglycerin-flicker test has revealed the presence of arterial hypertonus or spasm of the retinal arteries in 99 per cent of patients with existing hypertension or coronary arterial disease” (p. 1274). Further, they suggest that “the nitroglycerin-flicker test may prove to be a valuable diagnostic aid (a) for the presence of angina pectoris and coronary occlusion where the evidence is equivocal, (b) for the detection and management of persons who may later develop hypertension and coronary arterial disease” (p. 1275).

It is the purpose of the present article to examine these views and to present new data with a critical statistical analysis.

Analysis of the Krasno and Ivy Report

Krasno and Ivy make the basic assumptions, as a working hypothesis, that there is hypertonus or spasm in hypertension and in coronary arterial disease, that this condition is reflected in the retinal vessels, that the hypertonus or
spasm in the retinal vessels tends to be relieved by nitroglycerin, and that the tonus of the retinal vessels is indicated by the fusion frequency of flicker. However, Krasno and Ivy did not actually study the retinal vessels and do not even mention eyeground findings in their patients and subjects, the whole chain of reasoning being dependent simply on the observed response of the flicker fusion frequency to nitroglycerin.

Weekers and Roussel found that changes in the retinal vessels can be seen with the ophthalmoscope before there is a change in the fusion frequency of flicker. Even in patients with marked arteriosclerotic changes in the retinal vessels (grade III), the fusion frequency was usually only slightly below normal. It might be inferred, therefore, that the ophthalmoscope would be a better discriminator in these regards than the flicker apparatus. However, the clinical value of the nitroglycerin-flicker test is not necessarily dependent on the theory offered by Krasno and Ivy. The real question is the extent to which their test discriminates between diseased and healthy persons, and its possible use in predicting the appearance of frank disease in persons who are clinically healthy or who present an equivocal picture.

Krasno and Ivy reported findings on four groups: (1) 32 “normal,” clinically healthy persons between 20 and 50 years of age (mean age 27.8 years); (2) 208 “patients without evidence of cardiovascular disease”; (3) 216 patients with hypertension and/or coronary heart disease; and (4) 20 cardiac patients without evidence of hypertension or coronary disease. The sex composition of none of the groups was specified and the only information about the age in group 3 was the ranges of the clinical categories. Comparisons are somewhat hindered by the fact that the fusion frequency was reported in flashes per second for the “normal” subjects and in flashes per minute in the three categories of patients. Here we shall convert all data to flashes per second in keeping with the consistent practice in the previous literature.

No nitroglycerin tests were reported on the clinically healthy subjects but it was stated that they had a mean flicker fusion frequency of 44.5 flashes per second without the drug. The only relevance of this group seems to be to demonstrate that patients with hypertension or coronary disease tend to have low values for the fusion frequency of flicker. However, the patients without evidence of cardiovascular disease also had values of the fusion frequency quite comparable with those for the cardiovascular patients, except the group with malignant hypertension, but definitely lower than for the normal persons of equal age. This is consistent with the known fact that various types of pathology may depress the fusion frequency of flicker.

The real burden of Krasno and Ivy’s thesis rests on the comparison in the flicker fusion frequency response to nitroglycerin between the two categories of patients, those with and those without evidence of cardiovascular disease, and it must be noted that the latter were not clinically healthy or “normal.” Among these 268 patients who were considered as “cardiovascular normals,” the sublingual administration of 0.4 mg nitroglycerin was followed by no change or a decrease in fusion frequency in 206 patients and an increase in 62 patients. It was concluded that a decrease in fusion frequency is the “normal” response, and that an increase is an “abnormal” response. This conclusion apparently reflected the preponderance of responses and the fact that among the “abnormal” responders, papaverine or a second dose of nitroglycerin may produce a “normal” change (decrease) in fusion frequency of flicker. However, there is no mention of the effects with papaverine or a second dose of nitroglycerin in the patients who initially gave “normal” responses. Finally, it should be mentioned that papaverine treatment of 60 cardiovascular patients was followed by “normal” responses to the nitroglycerin-flicker test.

In contrast, all of the patients with hypertension or coronary heart disease responded to nitroglycerin with an increase in flicker fusion frequency. The type of pathology and the clinical picture did not seem to influence the magnitude of the change in fusion frequency. Among the 20 patients with cardiovascular disease but without evidence of hypertension...
or coronary disease, one patient (Buerger's disease) showed an increase in fusion frequency after nitroglycerin.

The data provided by Krasno and Ivy obviously provide no more than a suggestion that the flicker fusion response to nitroglycerin may have real diagnostic utility. The lack of tests on true "normals" for comparison, the variable results in the reference group of patients without evidence of cardiovascular disease, and the absence of statistical analysis are notable. We have attempted to remedy these defects in the studies reported below.

METHODS AND MATERIALS

The fusion frequency of flicker was determined by means of a newly developed electronic apparatus,12 which provides for the controlled variation of the brightness and of the light:dark ratio in addition to variation of the frequency.

The conditions of Krasno and Ivy's arrangement were reproduced as closely as possible. There was a slight difference in the color of the light source but this is considered to be without consequence. In the range of illumination used here, the color, when tested at the same brightness level, does not affect the fusion frequency of flicker.13 The electronically produced light flashes approach the ideal square wave form more closely than light flashes produced by mechanical interruption through rotating disks or cylinders, such as used in Krasno and Ivy's apparatus; it is inconceivable that such a difference would affect the results. Evidence of the degree to which we approximated Krasno and Ivy's procedure is a comparison of the normal means. The mean fusion frequency of Krasno and Ivy's group of 32 normal subjects from 20 to 50 years (mean age 27.8 years) was 44.5 flashes per second, and that of our group of 58 normal men from 48 to 58 years was 43.1 flashes per second. The slight difference is consistent with the known facts of the age trend.14, 15

The majority of our measurements were made in the sitting position but in some of our subjects the fusion frequency was measured in the supine position. The glow modulator tube in which the flicker is generated in our apparatus can be adjusted readily to any angle. There were two reasons for introducing the body position as a variable. First, it is known16 that the hemodynamic effect of nitroglycerin is affected by the body position so that a comparison of the supine and the sitting positions might be useful for the analysis of nitroglycerin effects. Second, as a method suggested for differentiation between patients with and without cardiovascular disease, standards should be provided for use at the bedside.

After a rest period of 10 minutes or more, the flicker fusion frequency was determined before and four and six minutes after sublingual administration of 0.4 mg. of nitroglycerin. All determinations were made in duplicate; analysis of the duplicate records showed a repeat variability of less than 0.5 flashes per second.

SUBJECTS

A total of 302 men were studied, comprising 47 controls, 145 clinically healthy ("normal") subjects and 110 patients with cardiovascular disease. The normal subjects ranged from 45 to 58 years and the patients were within a similar age range except for a few patients with rheumatic heart disease. The normal men have been under repeated observation in this Laboratory for a period of four years. They were screened as to absence of disease in thorough clinical examinations and various types of stress tolerance tests.17 Some of the cardiovascular patients were members of the same group who had developed cardiovascular disease in recent years and a few others were referred by private physicians; most of the patients were from the Minneapolis Veterans' Hospital.

RESULTS

The principal results are summarized in table 1. In the first place, dummy trials (controls) without nitroglycerin on 47 men established the repeat variability of the procedure as used in the nitroglycerin tests. The mean change was very close to zero (+0.02) and the standard deviation of the changes was ±0.68, that is in roughly two-thirds of the controls the second measurement of flicker fusion frequency without nitroglycerin was within the range +0.70 and −0.66 flashes per second. The administration of nitroglycerin to the clinically healthy men, both in the supine and in the seated position resulted in substantially identical results; the mean changes from pre- to postnitroglycerin did not differ significantly from the controls.

The same was true of the 58 patients with hypertension (rows 5, 6, 7 in table 1) and the patients with infarcts but without angina (row 9). In a more detailed analysis it was found that the response to the nitroglycerin-flicker test in patients with advanced hyper-
tension was not significantly different from that in patients with only mild to moderate hypertension. However, in the group of patients with angina pectoris (nine patients with a history of infarction and 13 patients with no evidence of infarction) there was a statistically significant (<0.01 probability of chance explanation) tendency to an increase in the fusion frequency of flicker after nitroglycerin.

In addition to the patients summarized in table 1, tests were made in the supine position on three patients with angina pectoris without infarction and on two patients with infarction

Table 1

The flicker fusion frequency (f.f.f.) and its response (Δ) to nitroglycerin. The controls were subjected to a dummy experiment, omitting the nitroglycerin. All values in flashes per second. S. D. = standard deviation.

<table>
<thead>
<tr>
<th>Group</th>
<th>Position</th>
<th>No.</th>
<th>f.f.f.</th>
<th>Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean S.D.</td>
<td>Mean S.D.</td>
</tr>
<tr>
<td>1. Control</td>
<td>Seated</td>
<td>47</td>
<td>42.3±0.02</td>
<td>+0.02±0.68</td>
</tr>
<tr>
<td>2. Healthy</td>
<td>Supine</td>
<td>87</td>
<td>46.7±0.40</td>
<td>-0.13±1.28</td>
</tr>
<tr>
<td>3. Healthy</td>
<td>Seated</td>
<td>58</td>
<td>43.1±0.20</td>
<td>+0.14±0.86</td>
</tr>
<tr>
<td>4. 2. + 3</td>
<td>—</td>
<td>145</td>
<td>—</td>
<td>-0.02±1.14</td>
</tr>
<tr>
<td>5. High B. P.</td>
<td>Supine</td>
<td>23</td>
<td>47.8±0.57</td>
<td>-0.17±1.46</td>
</tr>
<tr>
<td>6. High B. P.</td>
<td>Seated</td>
<td>35</td>
<td>41.9±0.50</td>
<td>+0.17±1.85</td>
</tr>
<tr>
<td>7. 5. + 6</td>
<td>—</td>
<td>58</td>
<td>—</td>
<td>+0.04±1.70</td>
</tr>
<tr>
<td>8. Angina</td>
<td>Seated</td>
<td>22</td>
<td>39.8±0.55</td>
<td>+1.90±2.41</td>
</tr>
<tr>
<td>9. Infarct, with-out Angina</td>
<td>Seated</td>
<td>7</td>
<td>41.1±0.56</td>
<td>-0.06±1.69</td>
</tr>
</tbody>
</table>

but no angina; their responses to the nitroglycerin-flicker test were within the normal limits as calculated from the data in line 2, table 1. Finally, tests were made on 10 patients with rheumatic heart disease (mostly with some degree of failure) and on seven patients with miscellaneous abnormalities in the electrocardiogram; all of these patients were likewise within the limits of the normal response.

The variability (S. D.) between the pre- and postnitroglycerin fusion frequency was somewhat greater than between the first and second tests in the control series. This means that in healthy men nitroglycerin administration introduces variable factors, probably in the blood supply to the visual pathways; this would be compatible with the rather complex circulatory situation after nitroglycerin.

Table 1 indicates that the variability of the change after nitroglycerin (ΔS. D.) was higher in all groups of patients than in normal men. Table 2 shows that these difference in the variability, tested by the F test, were statistically significant. This fact that nitroglycerin produces more variable results in patients than in healthy men has the result of interfering with the reliability of differentiation, with the nitroglycerin-flicker test, between healthy men and men with, for example, coronary insufficiency.

It was noted above that the response to the nitroglycerin-flicker test was substantially identical in the seated and in the supine positions. However, without nitroglycerin, that is in the initial measurement, the fusion frequen-

Table 2

Comparison of 58 "normal" men with the several categories of patients in regard to the variability, in the seated position, of the change in flicker fusion frequency after nitroglycerin. VR = variance ratio, patients:normals.

<table>
<thead>
<tr>
<th>Patients</th>
<th>No.</th>
<th>VR</th>
<th>Signif.</th>
</tr>
</thead>
<tbody>
<tr>
<td>High B. P.</td>
<td>35</td>
<td>4.66</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Angina</td>
<td>22</td>
<td>7.90</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Infarct, no angina</td>
<td>7</td>
<td>4.10</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

quency of flicker was lower in the seated position in both healthy men and in men with hypertension. This difference is statistically highly significant in both groups (p = < 0.01).

In a few trials with patients with angina pectoris and with myocardial infarcts a similar effect of posture was observed. These results suggest that in all persons there may be a more effective cerebral circulation in the supine than in the sitting position.

The means of the initial flicker fusion frequency in patients with arterial hypertension were not significantly different from those of the healthy subjects. However, when only patients with advanced hypertension were considered, the initial fusion frequency was significantly subnormal (mean = 39.1 flashes per second in seven patients in the seated position). The mean initial flicker fusion frequency was also distinctly subnormal in patients with angina pectoris as indicated in table 1. In 10 patients with rheumatic fever
heart disease, the initial flicker fusion frequency was markedly subnormal, the mean for seven patients in the supine position and three patients seated being only 36.8; most of these patients were in failure. This is in harmony with the earlier finding that the fusion frequency tends to be low in severe circulatory disorders, presumably because of relative cerebral hypoxia or ischemia.7

So far, we have discussed group means and general variability. This does not precisely answer the question as to the differentiation of individuals. Krasno and Ivy arrived at their conclusion that the nitroglycerin-flicker test differentiates 99 per cent of patients with hypertensive or coronary heart disease from the incidence of changes in the flicker fusion frequency without regard to their magnitude. A more valid procedure would be the comparison of the response of each individual patient with the normal range limits of the response in healthy persons.

Table 3 shows the expected range limits for 95 per cent and for 98 per cent of a normal (healthy) population corresponding to the men included in lines 2 and 3 of table 1. For example, consider a man tested in the seated position who had an initial flicker fusion frequency of 37.5 and after nitroglycerin a value of 39.0. In healthy persons an initial value this low would be expected in less than 1 in 100 men but an increase of this magnitude after nitroglycerin would be expected in more than 5 per cent of healthy men; a reasonable conclusion would be: “initial value probably subnormal, response to nitroglycerin normal.”

The numbers and percentages of our patients outside of these limits are shown in table 4; the values for each patient were compared with the range limits for the position in which he was tested. Attention should be directed first to the right hand side of table 4 which gives the results of the nitroglycerin test.

Only two out of 58, or 3.5 per cent, of the patients with arterial hypertension showed a definitely “abnormal” (p = 0.01) response in the sense used by Krasno and Ivy while the incidence of excessive decreases is, if anything,
somewhat greater. This means that the criterion of an increased fusion frequency in the nitroglycerin-flicker test failed to differentiate from healthy men more than 95 per cent of our patients with arterial hypertension. Moreover, after nitroglycerin only 8.6 per cent of these patients showed increases which would be labeled "possibly abnormal"; 5 per cent of a healthy population would be so classed.

The results of this analysis are somewhat more favorable in the patients in the coronary heart disease group (angina pectoris, myocardial infarct, or both). But even here the nitroglycerin-flicker test failed to differentiate 70 per cent of the patients from healthy men. Substantially the same result obtained when the men with angina and those with infarcts were considered separately.

For the 93 combined patients with hypertension or coronary heart disease a probably significant increase in flicker fusion frequency after nitroglycerin was found in 12 men, while an equally significant decrease was found in four men. The criterion of a probably significant increase was met by less than 13 per cent of the patients and that of a possibly significant increase by only 18 per cent of these patients.

The left side of table 4 shows the numbers and percentages of patients who fall outside of the normal range limits of the fusion frequency of flicker without nitroglycerin administration. The incidence of apparent abnormality in this regard is more impressive than the change after nitroglycerin. All of the patient groups show significant incidences of patients with low fusion frequencies, this being least striking in the patients with hypertension and most notable in the patients with valvular heart disease. In the combined 93 hypertension-coronary disease patients, 16 are below the low limit for 99 per cent of healthy men and 26 men fall in the "possibly subnormal" class.

These results suggest that the simple flicker fusion frequency measurement is at least as good as, and very possibly it is better than, the nitroglycerin-flicker test in the differentiation of hypertensive and coronary disease from the healthy state. We have tested the statistical significance of the differences, apparent in table 4, between the criterion of low fusion frequency and the criterion of increase after nitroglycerin as devices to differentiate patients from healthy men. The difference in favor of the simple flicker fusion frequency test could arise by chance in roughly one out of six trials.

**Discussion**

A full explanation of the difference between our results and those reported by Krasno and Ivy cannot be offered. One obvious factor is the great disparity between the findings on our group of healthy men and their findings on their reference group, that is patients without evidence of cardiovascular disease. We cannot agree that a decrease or no change in the fusion frequency of flicker after nitroglycerin is the "normal" response since we found that an increase was as frequent as a decrease in these healthy men. It could be suggested, of course, that a decrease is characteristic of sick people who do not show evidence of major cardiovascular disease. In any case it is difficult to understand the justification in discarding the results on 62 of the "cardiovascular normals" of Krasno and Ivy simply on the ground that they did not conform to the majority findings.

The difference between our findings and those of Krasno and Ivy on cardiovascular patients is more puzzling. They reported a uniform increase in the fusion frequency of flicker after nitroglycerin in this category. We found a tendency in this direction in patients with angina pectoris, but it was very far from being uniform. And in hypertension there was not even a tendency to increase. The majority of our patients were not very ill and it is possible that the patients studied by Krasno and Ivy represented, on the average, more advanced stages of disease, but it is inconceivable that the clinical status of the two series did not overlap to a considerable extent.

The most important question raised by Krasno and Ivy is the possible value of the nitroglycerin-flicker test for the early detection of cardiovascular disease, particularly at the subclinical stage. We were unable to discover the slightest support for this view in our own
work. Although we found some patients who had a considerable increase in flicker fusion frequency after nitroglycerin, these were few and represented, in general, well established cardiovascular disease.

Krasno and Ivy reported no analysis of the magnitude or significance of change in the flicker fusion frequency after nitroglycerin and apparently considered only the direction of change. In our own series, if no account is taken of the magnitude or significance of the change, it is found that a considerable proportion of the patients did have higher values for the fusion frequency after nitroglycerin. But a considerable proportion of our healthy men also had higher values after nitroglycerin and even in the control series, where no nitroglycerin was administered, 44.7 per cent of the second fusion frequency measurements were above the initial fusion frequency. Table 5 summarizes the data analyzed in this way.

There are obviously no significant differences between the controls, the healthy men, or the men with hypertension, in the percentages of "abnormal" responses in the sense used by Krasno and Ivy. Statistical tests showed, likewise, that there is no significant difference between the incidence of "abnormal" responses in the healthy men and the combined group of those with hypertension or coronary disease. Only the patients with angina pectoris differed significantly from the healthy men in the incidence of the so-called abnormal response. The difference in this latter case is small, however; with equal numbers of angina patients and of healthy men there would be only 1.3 times as many "abnormal" responses in the patients as in the healthy men.

In our hands, at least, the nitroglycerin test is completely useless in discriminating hypertensive patients from healthy men; random guesswork would serve equally well. But it is useful to see what results we should expect, using the criterion of "abnormality" proposed by Krasno and Ivy, in discriminating patients with angina pectoris from healthy men in a mixed group presented for diagnosis.

For this purpose we may use the simple computation procedure recently applied (Keys\textsuperscript{18}) to another proposed discrimination device. Suppose we have a population made up of 900 healthy men and 100 men with coronary insufficiency. The nitroglycerin-flicker test will result in finding "abnormal" responses (that is, increases, as in table 5) in \(0.43 \times 900 + 0.74 \times 100 = 461\) men, of whom only 74 would actually be diseased. There would be 26 diseased men missed and 387 healthy men incorrectly labeled "coronary disease." There would be 415 diagnostic errors in "finding" the 74 diseased men.

It may be suggested, of course, that some of the "healthy" men used in the present studies are actually unrecognized cases of coronary disease and therefore the true incidence of "abnormal" responses in completely healthy men is less than we found. While this is conceivable, it is inconceivable that undiscovered or latent coronary disease exists in more than a small fraction of our men who were pronounced "healthy" after prolonged observation and very elaborate tests and measurements. But, suppose that 10 per cent of our healthy men are actually cases of latent coronary disease and that such latent cases have the same response to the nitroglycerin-flicker test as the men with frank angina pectoris. We can then calculate the incidence of abnormal responses in truly healthy men as follows.

Among 1000 men clinically considered to be healthy, there would be 100 who are hidden cases of coronary disease and of these latter there would be 74 men who would have an "abnormal" response to the Krasno-Ivy test. But in the entire 1000 men there would be 430

<table>
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<th>Category</th>
<th>-</th>
<th>0</th>
<th>+</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Controls</td>
<td>42.6</td>
<td>13.7</td>
<td>44.7</td>
</tr>
<tr>
<td>2. Healthy</td>
<td>39.7</td>
<td>17.2</td>
<td>43.1</td>
</tr>
<tr>
<td>3. Hypertension</td>
<td>42.9</td>
<td>11.4</td>
<td>45.7</td>
</tr>
<tr>
<td>4. Angina</td>
<td>21.7</td>
<td>4.4</td>
<td>73.9</td>
</tr>
<tr>
<td>5. 3. + 4.</td>
<td>34.4</td>
<td>8.7</td>
<td>56.9</td>
</tr>
</tbody>
</table>

Table 5.

Percentages of men who had lower (-), no change (0), and higher (+) values for flicker fusion frequency after nitroglycerin (or in the dummy second trial in the controls) than in the initial measurements.
abnormal responders, of whom 430 - 74 = 356 would be in the 900 truly healthy men. The percentage of abnormal responses among truly healthy men would then be 100 \times 356/900 = 39.5.

We may now repeat the computation to find the results of application of the Krasno-Ivy test with this revised estimate for healthy men. In a population of 1000 men made up of 900 truly healthy men and 100 cases of latent coronary disease we would “find” 74 of the 100 diseased men and would erroneously apply the label “coronary disease” to 320 of the 900 truly healthy men. There is a total of 346 diagnostic errors, or a ratio of roughly five errors to each correctly positive diagnosis. The foregoing computation is, we believe, the most favorable estimate for the validity of the test we can make.

From table 5 it is indicated that the simple measurement of flicker fusion frequency without nitroglycerin is not inferior to the Krasno-Ivy test as a means of discriminating patients from healthy men. With the simple measurement of fusion frequency alone the criterion is a subnormal value for flicker fusion frequency.

Independent of any factor of disease or effect of nitroglycerin, there will be, of course, a tendency for low values of the initial fusion frequency to be associated with increases after nitroglycerin. This follows from the fact that there is a random “error” in such measurements, partly from true error in measurement and partly from random fluctuations in the ability of the subject to see and report correctly the fusion point. If the initial fusion frequency measurement happens, by such random error, to be lower than the subject’s true mean fusion frequency, the chances are that a succeeding measurement will be higher (law of the tendency toward the mean).

Among the increases (and decreases) after nitroglycerin there must be at least some artefacts of this kind. Their frequency and importance may be estimated with the help of the data in the control series when no nitroglycerin was given. We have calculated, by least squares, the value of the slope b in the regression equation, \( y = a + bx \), where \( y = \) the change in flicker fusion frequency after nitroglycerin and \( x = \) the prenitroglycerin flicker fusion frequency. For the control series \( b = -0.108 \) and this is statistically highly significant. The alternative calculation of the correlation coefficient gave a value of \( r_{xy} = -0.32 \) for this control series. Similar calculations with the data for the patients with hypertension and with angina pectoris gave values for \( b \) of \(-0.177\) and \(0.198\), respectively. These slopes prove to be not significantly different from that in the control series. In other words, the inverse correlation between the initial flicker fusion frequency and the change after nitroglycerin in these series may be explained by the regression toward the mean observed in the control series.

**Table 6.**

Incidence of “abnormal” flicker fusion frequency results (outside the 98 per cent normal range limits) in men with coronary disease. “Initial” = subnormal value before nitroglycerin, \( \Delta \text{f.f.f.} \) = abnormal rise after nitroglycerin.

<table>
<thead>
<tr>
<th>Category</th>
<th>Total Men</th>
<th>Initial</th>
<th>( \Delta \text{f.f.f.} )</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina</td>
<td>16</td>
<td>2</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Infarct</td>
<td>19</td>
<td>10</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>12</td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>

This relative absence of correlation suggests that the initial flicker fusion frequency and the response to nitroglycerin are relatively independent criteria for discriminating between coronary patients and “normals” and might, therefore, be combined to yield a more effective discrimination. In table 4 it was noted that out of 35 coronary patients there were 12 men who showed significantly subnormal values for the initial fusion frequency and 10 men who showed significant increases in fusion frequency after nitroglycerin. On inspection of the data, however, it was found that only five of these men were abnormal in both regards and that a total of 17 of these 35 coronary patients were significantly abnormal with one or the other criterion. If both criteria are applied, with the 98 per cent limits given in table 3, we find that 48.5 per cent, instead of 28.6 per cent, of the coronary patients are
abnormal in the sense that they differ from 99 per cent of clinically healthy men.*

In the course of tabulating the data on the coronary patients for the analysis with both criteria (that is, initial fusion frequency and Δ fusion frequency after nitroglycerin), it was observed that the patients with angina but without evidence or history of infarction appeared to behave differently from the patients with infarcts. The men with angina but without infarcts tended to be more abnormal in response to nitroglycerin than in their initial flicker fusion value. On the other hand, the men with infarcts tended to be more abnormal initially than in their response to nitroglycerin.

The data which are summarized in table 6 were treated statistically by the exact contingency analysis† from which it was found that the probability of chance explanation of the differential behavior of “angina” and “infarcts” summarized in table 6 is only 0.0479; the crude chi square approximation gave a value of 0.03 for this probability. The desirability of further research along these lines is obvious.

It will be recalled that Krasno and Ivy began their study of the nitroglycerin-flicker test on the theory that vasoospasm, which would be relieved by nitroglycerin, may be present in cardiovascular patients. The findings here give no support to this theory except, perhaps, in the patients with angina pectoris. There is certainly no evidence from these data for vasoospasm in the hypertensive patients, much less that vasoospasm, discernible by this method, may precede the appearance of clinical hypertension.

Finally, it is well to point out that the strictures on the utility of the nitroglycerin-flicker test for discovering cardiovascular disease do not mean that flicker fusion frequency measurements have no utility in studying patients with suspected or actual circulatory disorders. So far as it goes, the data here confirm previous findings that the fusion frequency of flicker is sensitive to deficiencies in the circulation, particularly that of the brain.

* Note that with the 98 per cent limits there will be 1 per cent beyond each end of the range.

Summary

1. An analysis has been made of the report by Krasno and Ivy that the response of the flicker fusion frequency (f.f.f.) to sublingual nitroglycerin不同iates cardiovascular patients with hypertension or coronary disease from persons who are clinically healthy or normal.

2. Data are reported on the flicker fusion frequency before and after nitroglycerin in 145 clinically healthy, “normal” men and in 110 men with cardiovascular disease. Data are given also on 47 men who served as controls in dummy experiments. Studies were made both in the seated and in the supine position.

3. Fiducial tables are presented for the range limits of the initial flicker fusion frequency and its change after nitroglycerin within which it is predicted 95 per cent and 98 per cent of clinically healthy, “normal” men will be found.

4. The claim that the Krasno-Ivy nitroglycerin-flicker test may be a useful discriminator for detecting or evaluating hypertensive or coronary disease is not confirmed.

5. In clinically healthy men increases in flicker fusion frequency after nitroglycerin were just as frequent as were decreases and a similar result was obtained with patients with hypertension.

6. About 30 per cent of patients with coronary disease showed a significant increase in flicker fusion frequency after nitroglycerin. An equal, or larger, percentage of these patients showed prenitroglycerin fusion frequency values which are significantly subnormal.

7. All categories of men showed higher fusion frequency values in the supine position than in the upright position but the response to nitroglycerin was substantially the same in both positions.

8. The present data and analysis indicate that the simple flicker fusion frequency measurement is not inferior to the nitroglycerin-flicker test in differentiating cardiovascular disease and that neither test can be recommended as a screening or detecting device for individuals.

9. The possibilities of using both initial
flicker fusion frequency and the change after nitroglycerin as discriminating criteria are discussed.

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The Flicker Fusion Frequency and Its Response to Nitroglycerin in Normal Subjects
and in Patients with Cardiovascular Disease
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