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A Comparison of Economic, Administrative, Patient Preference, and Predictability Involving Three Methods of Dry Eye Determination

Abstract: Our study involved a comparison of economic, administrative, patient preference, and the predictability of determining dry eye symptoms in 30 patients. The three tests compared were the Schirmer modified test, the Lactoplate Lactoferrin Immunoassay test, and the not as yet available in the U.S., Cotton Thread Tear test developed by Hamano, et.al. 100% of the patients preferred the Cotton Thread test compared to the other two tests, while 80% preferred the Schirmer over the Lactoplate. A subjective survey of patient discomfort induced by the testing procedure (based on a scale of 0 - no discomfort to 10 - extreme discomfort) revealed a Lactoplate mean of 7.43, Schirmer of 5.53, and a Cotton Thread mean discomfort level 0.93.

Economic factors included test cost, test shelf life, and the total amount of practitioner time necessary for the test. There was a large disparity between the Schirmer and Cotton Thread Tests, which involved minimal practitioner time and cost (the exact cost of the Cotton Thread test was not ascertained at this time, but should be comparable to the Schirmer, based upon the simplicity of the material), and the Lactoplate which involves a significant increase in time and cost, and which has a limited shelf life.

A subjective measurement of the ease of practitioner test administration and patient cooperation (based on a scale of 0 - very easy to 10 - very difficult) revealed a Lactoplate mean of 2.80, a Schirmer mean of 1.43, and a Cotton Thread mean of 0.48.

Two methods of predictability were employed. The first compared the subjective symptoms with the objective findings using the established cut-off for definitive dry eye. With this method the Schirmer Test demonstrated the highest level of predictability with a sensitivity of 50% and a specificity of 86.36%. This compared with a Lactoplate sensitivity of 12.5% and a specificity of 100%, and a Cotton Thread sensitivity of 12.5% and specificity of 95.45%.

The second method involved a comparison of the means and standard deviations of the test results of asymptomatic versus symptomatic patients. Utilizing this method, the mean of the symptomatic group was greater than one standard deviation below the mean of the asymptomatic group for all three tests.

Introduction: Approximately 20-25% of patients seen in an eye clinic complain of dry eye. There are a number of different factors which may contribute or exacerbate this condition including tear film deficiencies and dysfunction, exposure keratitis, neurotrophic keratitis, corneal epithelial disorders, systemic conditions and disease, ocular and systemic medications, environmental factors, and contact lens wear. Diagnosing the underlying cause of dry eye requires a careful case history,

gross external and biomicroscopic examination. Historically a number of test procedures have been used to aid in dry eye diagnosis. These include tear break up time (BUT) developed by Norn in 1969 using fluorescein, rose bengal staining, and the Schirmer Test. Each of these methods has its limitations and drawbacks, the Schirmer Test has demonstrated poor sensitivity and specificity, poor reproducibility, a non-gaussian distribution of wet lengths for a normal population, irritation, and corneal epithelial cell shrinkage, and a long test time (five minutes). Rose bengal staining has demonstrated a poor sensitivity, irritation, and false positives for patients with conjunctivitis. Similarly the fluorescein break-up time test has demonstrated poor reproducibility, intersubject variability, and by its nature affects tear surface tension, secretion and evaporation rates. Fluorescein has been shown to decrease tear break-up time by up to 30 fold.

More recently new test procedures have been developed in the attempt to improve accuracy and efficiency. These include non-invasive tear break-up time (NIBUT) as measured with a toposcope as demonstrated by Mengher et al in 1985. This method has a sensitivity of 82% and a specificity of 86%, and demonstrated a significantly lower ($P<0.001$) NIBUT's for symptomatic subjects versus normal subjects. The major drawback involves the purchase of the toposcope and the time involved in becoming proficient in its use. Tear osmolarity has been shown to have a variable sensitivity and specificity depending upon the study, but the technique has been found to be too difficult for employment in a clinical setting. Another recent investigative method is conjunctival impression cytology which involves fixing and staining epithelial and goblet cells for microscopic inspection. This method has demonstrated a sensitivity of 100% and a specificity of 87% (Nelson and Wright, 1986a). This method would also be difficult to adapt to a clinical optometric setting.

Additionally a method for measuring tear lactoferrin concentration has become commercially available. This method has demonstrated good accuracy and precision (manufacturer's data), with one study demonstrating a 35% sensitivity and a 70% specificity, but has definite drawbacks which will be discussed in this paper. Yet another recently developed (Hamano, 1982) method is the phenol red cotton thread tear test, which has definite advantages over the previously discussed methods. Asbell (1987) found the cotton thread test to be statistically more reliable, with less variation and more sensitivity to small variations, than the Schirmer test.

In this study we investigated three methods for determining dry eye in regards to economic and administrative factors, patient preference, and test predictability. The three tests were the cotton thread test, the lactoplate, and a modified Schirmer test. Additionally we investigated the effect of age on lacrimal gland function as measured by the tests.

Materials and methods: This study was conducted at the Ferris State College of Optometry in Big Rapids, MI. All test subjects consisted of optometry students, faculty, relatives, and patients seen in the clinic. Thirty individuals, ranging in age

from 11 years to 44 years, were tested using each method. Testing consisted of administering the cotton thread O.D., followed by the lactoplate O.S., and lastly the modified Schirmer O.D.. It was believed that this method would allow for tear concentrations to return to baseline levels O.D. for the Schirmer measurement since the cotton thread test uses only 10% of the tear volume used by the Schirmer. The cotton thread was administered (O.D.) using forceps with the 3mm crimped end inserted into the inferior conjunctival sac temporally. The patient was asked to close their eyes for the 15 second test duration, at which time the lower lid was pulled down and the thread removed. After all capillary action had ceased the thread was measured, including the 3mm crimped end, using a millimeter rule.

The lactoplate was then administered to the opposite eye (O.S.). This method involves the insertion of a paper disc into the temporal inferior conjunctival sac for a 2 minute duration. The manufacturer (Eagle Vision) suggests a 2-5 minute duration, or until the disc is moistened. The disc is removed using forceps then blotted to remove excess fluid at which time it is gently pressed into the prepared gel. The results in the form of a ring of reactivity between the enzyme and the gel are obtained after a 3 day incubation at room temperature. This data is then converted using a formula into lactoferrin concentration.

The Schirmer was then administered O.D. using a technique modification, where in the testing duration is one minute compared to the normal five minutes, and the test result is multiplied by three. This modified method decreases the testing time and shows good correlation to the five minute method (reference?). A paper test strip was inserted into the temporally into the lower conjunctival sac in a manner similar to that stated for the other techniques. The patient then closed their eye and after one minute the strip was removed and the wet length was recorded after capillary action had ceased.

In addition to recording the measured values the test administrator also recorded the total test time involved in the procedure, the ease of test administration taking into account patient cooperation and quantified on a scale of 0 (very easy) to 10 (very difficult). Any ocular effects caused by the testing procedure, such as hypersensitivity reaction or trauma, were also noted. The test administrators consisted of 20 optometry students and 2 faculty.

At the conclusion of testing the patient was asked to fill out a survey as to test preference, the discomfort level of each of the tests quantified using a scale of 0 (no discomfort) to 10 (extreme discomfort), and whether they had dry eye symptoms. They were asked to quantify their symptoms, if present, using a scale of 0 (mild) to 10 (extreme). The age of each patient was recorded on their data sheet.

Results: The average wet thread length for all patients was 23.87, with a standard deviation of 9.05, Figure 1. We also determined the average wet length of the symptomatic and asymptomatic patients for dry eye with the results shown in Figure 1. Additionally listed are the results for those 6

patients under 14 years of age, who demonstrated significantly (p level?) higher results for each of the three tests. Figure 2 shows the results obtained from the Schirmer test, and Figure 3, the results of the lactoplate. In each of the three tests the mean of the symptomatic group was greater than one standard deviation below the mean of the asymptomatic group. This difference was most evident in the Schirmer test where the asymptomatic mean was 278% greater than the symptomatic mean. The thread test demonstrated a 61% difference, while the lactoplate showed a change of 21%. Figure 4 shows the data for the symptomatic patients. The asterik symbol denotes a positive finding of dry eye according to the tests parameters. The Schirmer test correctly identified 4 of the 8 symptomatic patients, but had three false positives. This corresponds to a sensitivity of 50% and a specificity of 86.36%. The lactoplate positively identified 1 of the 8 symptomatic patients, but had zero false positives,giving a sensitivity of 12.5% and a specificity of 100%. The thread test found 1 of the 8 patients with symptoms with one false positive with a resultant sensitivity of 12.5% and a specificity of 95.45%. As figure 4 shows the 3 tests combined found 6 of the 8 symptomatic patients, although no individual had a positive finding for more than one test. The two individuals that were not correctly identified had results below the mean average values for each of the three tests. 33% of the patients over age 14 were symptomatic for dry eye, with an mean discomfort level of 2.75 (Figure 4).

With regards to test preference 100% of the patients preferred the thread test over the other two tests, while 80% preferred the Schirmer over the lactoplate. A subjective survey of patient discomfort and practitioner ease of test administration showed a patient and practitioner preference for the thread test, followed by the Schirmer and then the lactoplate (Figure 5).

The Schirmer test cost is $10.50 for 100 individually wrapped test strips, or a per patient cost of $0.21. The test strips have a expiration date 4 years from the date of manufacture, both of which are labeled on the box. The box containing the strips is small, approximately 4 x 2 x 1 inches, and is designed for easy removal of individual strips. A dispenser stand is also available from the manufacturer. The instructions are printed on the box, and are readily understandable. The Schirmer, according to the manufacturers directions is a non quantifiable test, answering only yes or no to reduced tear secretion, with the strip being left in place until the 10mm notch is wetted. They suggest that the 10mm mark should be reached within 3 minutes, with 5 to 10 minutes requiring a further test after a suitable interval (not stated) and a time greater than 10 minutes indicative of a reduced tear secretion. The manufacturer does not recommend the use of an anesthetic, although this is used in the Schirmer test #2.

The lactoplate available from Eagle Vision has a cost of $200 for 16 units, or $12.50 per patient. It requires a 3 day incubation period before the results are known. The test time is variable, depending upon the amount of time necessary to completely wet the paper disc, with a maximum suggested time of

five minutes. The procedure has 10 steps and necessitates the use of forceps, and refrigeration of the test kits (at 4 C) prior to use. Use of an anesthetic is not recommended. The lactoplate comes with an instruction pamphlet which is very detailed with photographs and an 18 item bibliography. The lactoplate has a shelf life of approximately one year from the date of manufacture.

The cotton thread test is not yet available in the U.S. and we were unable to obtain an estimated cost per individual for this test. Based on the simplicity of the material used we anticipate a cost and shelf life similar to the Schirmer test (Sno strips). The thread test takes 15 seconds and requires no additional equipment or incubation time. The test can be repeated in the same patient visit because of the small quantity of tear film utilized (1/10th of the volume used by the Schirmer on average). The permanent change in color of the strip also results in a permanent record for future comparison.

Adverse ocular effects induced by the test procedure were reported only in one instance for the lactoplate, where an inferior subconjunctival heme resulted from injury with the forceps used to remove the paper disc. The patient was 11 years old and was uncooperative.

Discussion: The lactoplate scored the lowest for all aspects of our testing. It was a poor predictor of dry eye, was costly, time consuming, irritating to the patient, and necessitated special handling (refrigeration). In addition the lactoplate gel contains sodium azide which is highly toxic, reacting with acids to form a toxic gas and with metals to form a volatile explosive. It should also be noted that the lactoferrin test measures a tear enzyme concentration and not a tear volume, although a good correlation has been demonstrated between the two. Additionally there is variability associated with potent[illegible] differences in gel and paper characteristics between test kit[illegible] (though less than 5% and 10% respectively) according to the manufacturer. Why then have the lactoplate? The lactoplate is designed primarily to identify KCS (keratoconjunctivitis sicca) patients According to van Bijsterveld, the lysozyme test was found to be superior to the Schirmer and Rose Bengal tests in diagnosis of KCS. Additionally Meyer demonstrated that the dysfunction of the lacrimal gland in patients with KCS causes a decrease of lysozyme concentrations in their tears. It therefore appears that the use of the Lactoplate should be limited to those individuals symptomatic for dry eye who are good candidates for having KCS, i.e. individuals over 50 years of age with women predominating in incidence over men. Our study population had no test individuals in this age group so it is not surprising that the lactoplate demonstrated only a 12.5% sensitivity. As an aside we tested a known KCS patient aged 68, who demonstrated a positive lactoplate finding. We therefore recommend judicial use of the lactoplate, possibly in circumstances where permanent punctal occlusion is being considered. The Schirmer test performed best according to its manufacturer parameters in predicting dry eye. It was however out performed by the thread test in all other areas (with cost still being an unknown). The

Schirmer test is also more susceptible to reflex tearing due to the greater irritation caused by the paper strip compared to the thread. In our study the Schirmer demonstrated the most false positives which led to a decreased specificity compared to the other tests. An anesthetic has been used with the Schirmer, but this has led to additional problems with the validity of the test. The Schirmer test also requires the use of saline to wet the paper strips with the subsequent possibility of staining of clothing or the carpeting. In addition, studies have shown that the Schirmer has demonstrated poor performance as stated in the introduction.

The alternative then is to adopt the thread test, which performed the best in all categories except sensitivity. However, the criteria for dry eye of 9mm or less is based upon a study of Japanese patients. The mean for 3,780 normal eyes in Japan was 16.7mm, which contrasted with our mean of 26.55mm for asymptomatic patients, and a mean of 16.5mm for symptomatic patients. This suggests a possible cross-cultural difference with a probable correlation with morphology. Orientals have a prominent epicanthal fold which may decrease tear evaporation, due to decreased exposed conjunctival surface area. They also may have a smaller conjunctival sac area due to tighter lid adhesion. Additional factors may be environmental variations or differences in the study populations. Supporting our data is a soon to be published joint study involving the Univ. of Missouri-St. Louis School of Optometry and the Dept. of Ophthalmology of the Tokyo Women's College. Their results demonstrated a mean wetting length of 1112 American eyes of 25.3mm. This study also found a variation in wetting length with age with younger individuals demonstrating a longer mean wet thread length, 31.3mm for the 3-9year old cohort and, compared to a mean length of 21.8mm for the 60 and older cohort. This suggests the need for a cut off value which considers both culture and age. For example, if the cut off for the thread was set at 18mm in our study, the sensitivity would be 87.5% with a specificity of 77.3%.

Finally, the relative importance of these tests must be addressed. What are the treatments for dry eye? The major treatment is artificial tears. At a recent visit to an ophthalmological practice, the corneal specialist prescribed artificial tears to 13 of 17 patients based on subjective symptoms unsubstantiated by any testing. We recommend the use of single vial preservative free artificial tears to avoid contamination and allergic sensitivity to the preservative. We recommend the development of an aerosol artificial tear, which would allow for a preservative free multidispensing vehicle.

Another method of therapy is punctal occlusion, which can be tried on a trial basis with collagen plugs which dissolve in one week. The main clinical consideration appears to be in regards to successful contact lens wear. A patient who has a decreased tear quantity as measured by the thread test can be counseled to the possibility of unsuccessful contact lens wear, resulting from inadequate patient tear film and independent of practitioner knowledge or performance in fitting.

We foresee the successful introduction of the cotton thread test, replacing the Schirmer, with the lactoplate retaining its

value as a speciality test for KCS.

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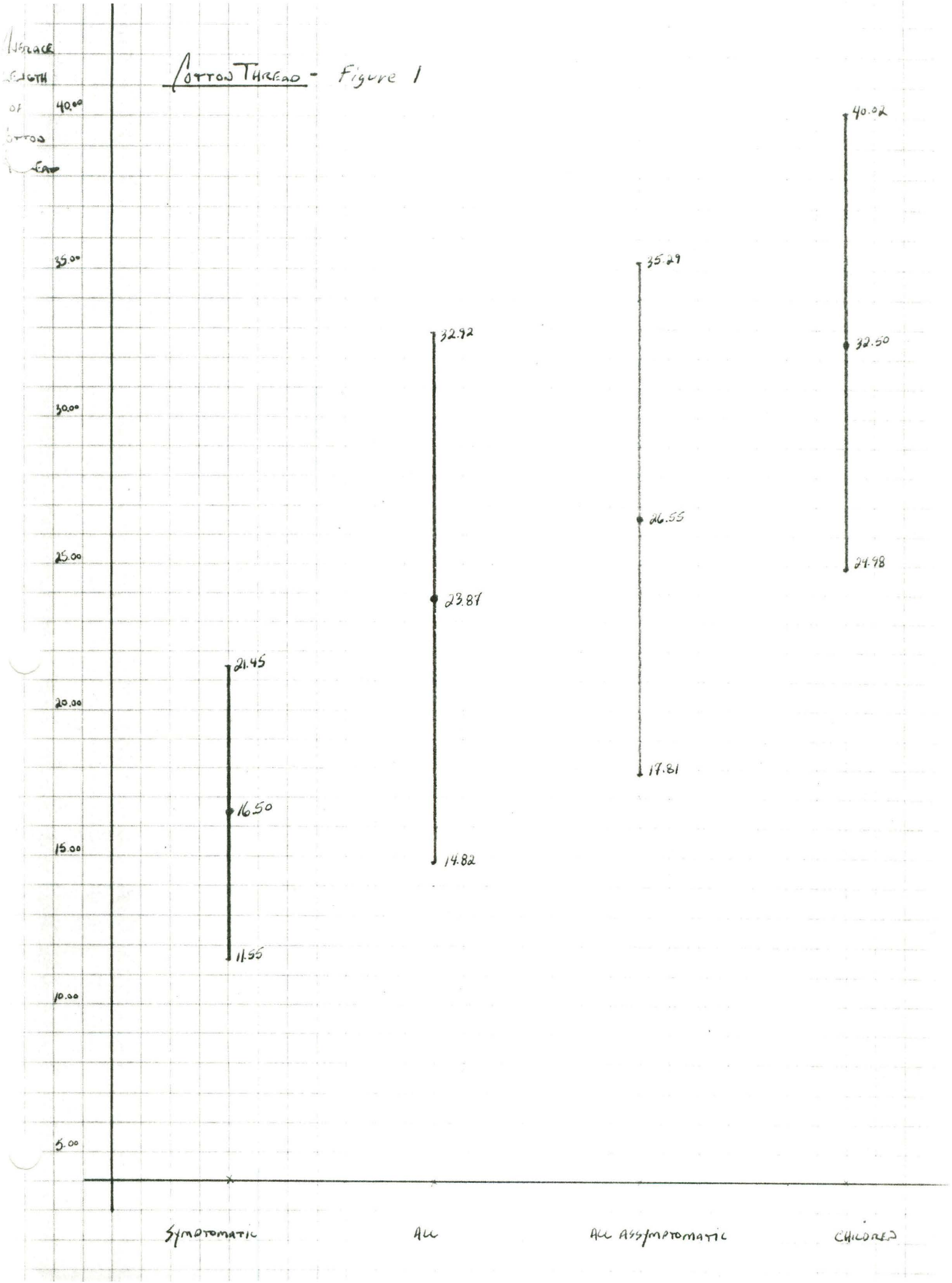
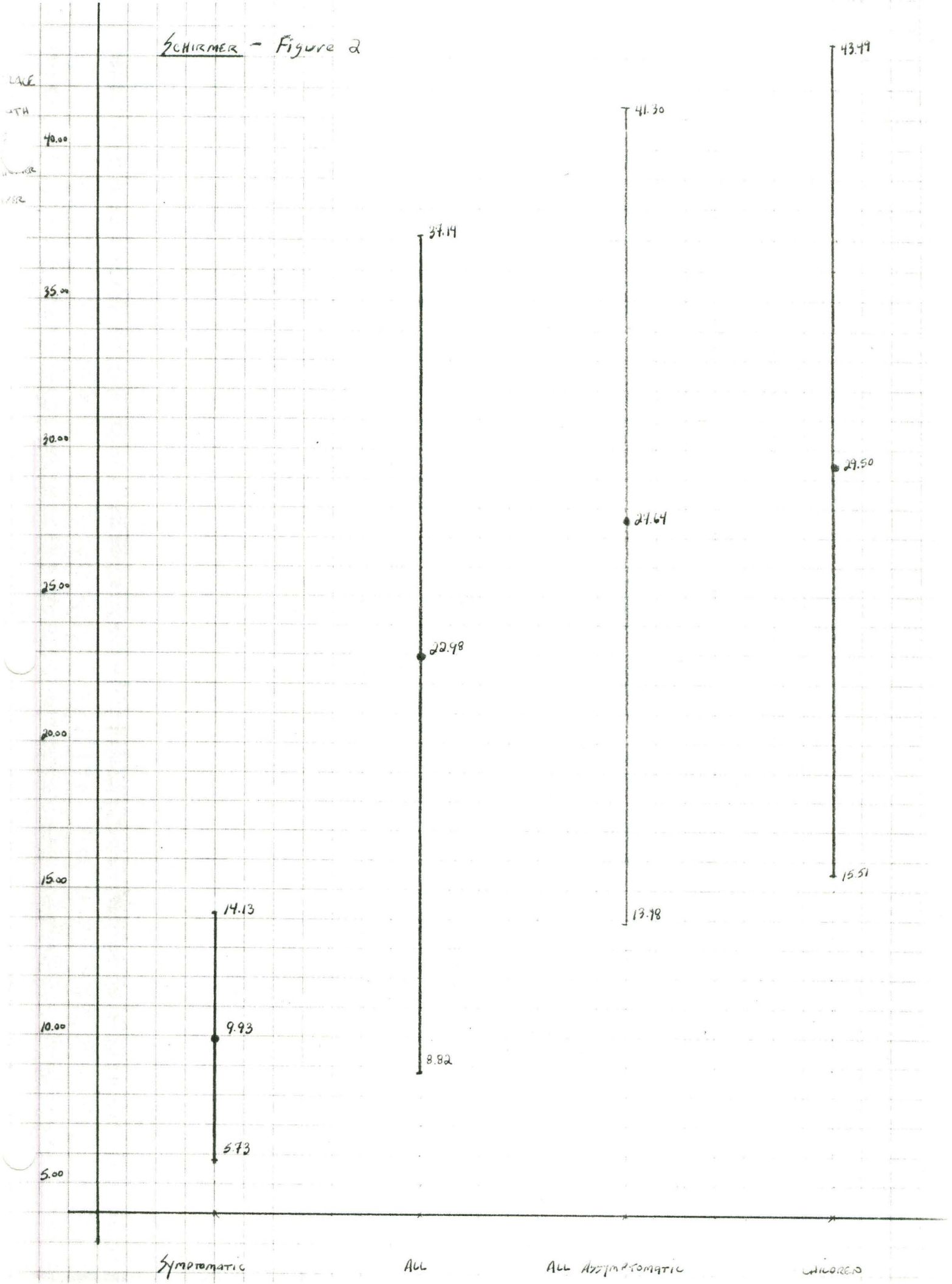
Average length of cotton fiber

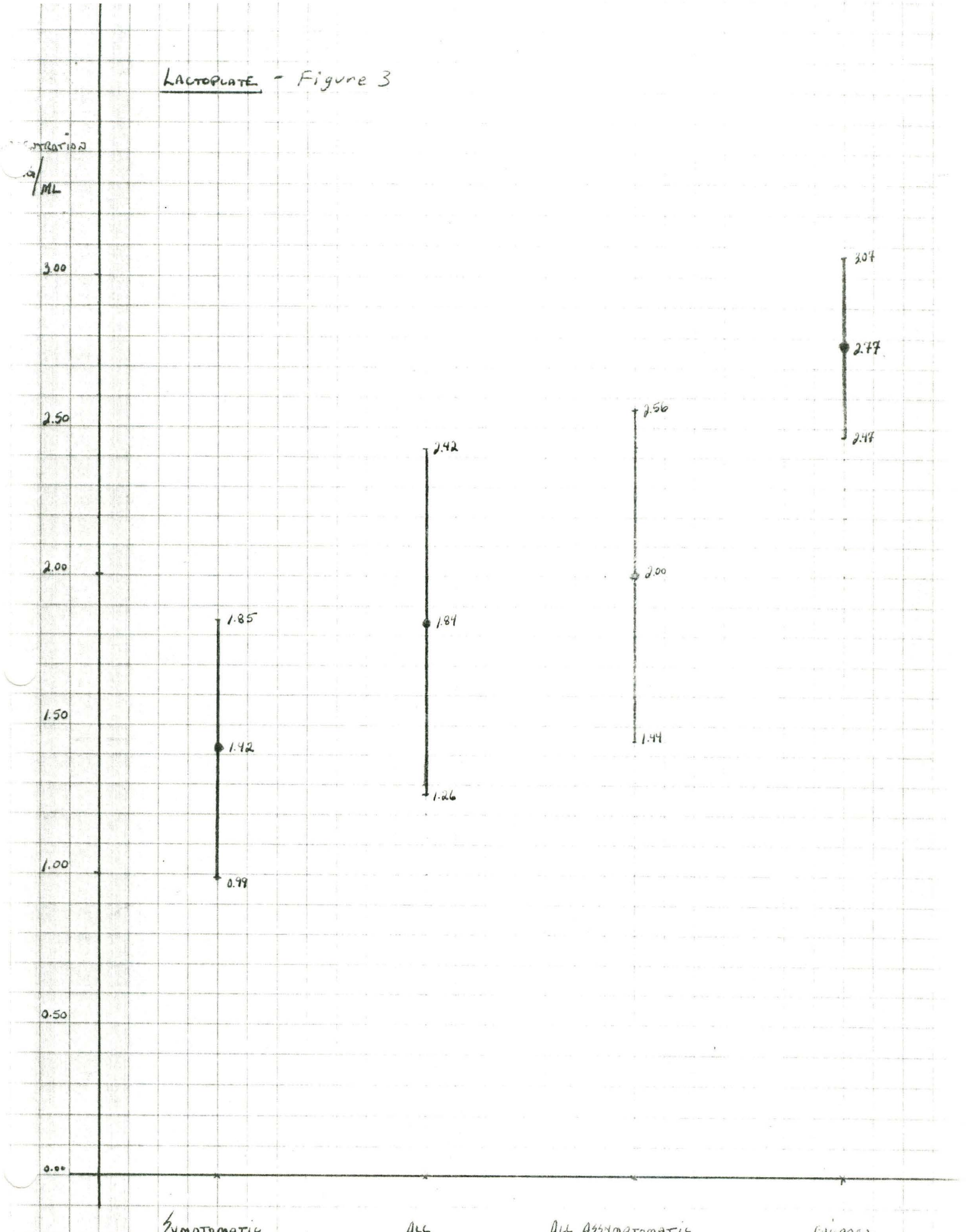
Cotton Thread - Figure 1



SCHIRMER - Figure 2



LACTOPLATE - Figure 3



PROFILES of SYMPTOMATIC DRY EYE PATIENTS

	AGE	SYMPTOMS #	THREAD	SCHIRMER	LACTOPLATE
1.	24	0	27	6.0*	1.40
2.	22	1	16	9.0*	1.50
3.	24	2	17	10.5	1.17
4.	25	2	18	18.0	1.80
5.	23	3	9*	12.0	1.17
6.	22	3	17	12.0	0.79*
7.	44	5	15	3.0*	2.30
8.	31	6	13	9.0*	1.27

Ranked by Subjective Degree of Symptoms 0 = Mild to 10 = Severe

* Positive Objective Dry Eye Finding According to Manufacturer Parameters