Evaluation of Cholesterol Determinations Among Clinical Laboratories in Wisconsin

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THE INCREASING number of requests to clinical laboratories during the past 10 years for serum cholesterol determinations reflects the growing awareness by physicians of the possible relationship between serum cholesterol levels and cardiovascular disease. Greater numerical demands and the rapid growth of interest in laboratory studies related to cardiovascular disease have led to concern, among physicians and laboratory directors alike, regarding the stability of cholesterol levels as determined in a given laboratory and the comparability of determinations of this lipid among various laboratories (*1–3*).

At the 1957 Conference of Longitudinal Cardiovascular Studies (*1*), it was recommended that a national laboratory be established to initiate and conduct a study of cholesterol and to evaluate the various methods employed in its determination. The National Communicable Disease Center, Public Health Service, Atlanta, was chosen to carry out such a program, which would be open to the participation of State public health laboratories. A similar program was designed by the State Laboratory of Hygiene (*4*) to evaluate cholesterol testing in clinical laboratories in Wisconsin. The Wisconsin program is open to any interested laboratory in the State, and it is conducted on a voluntary basis without cost or obligation to the participants.

The Wisconsin cholesterol external quality control program began in December 1964, and it is continuing at the present time. This report summarizes the results obtained in the first phase of the program, the 2-year period through November 1966. The number of active participants has varied, with 87 registered at present. For statistical evaluation in this report, however, the work of 69 laboratories is considered, since the data collected on the remaining laboratories are insufficient to provide reliable conclusions.

The original purpose of the cholesterol external quality control program was not to establish approved or standard methods or to establish standard levels of performance. Rather, its major aim is to obtain performance data and to compute, evaluate, and report these data con-

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fidentially to the participants. This information can be used by each laboratory director to help improve or maintain the performance levels in his laboratory. The program offers the laboratory director an accurate, independent measure of the precision, stability, and accuracy of the cholesterol analyses conducted in his laboratory. It further enables him to ascertain how his laboratory's results compare with others in the State and, more important, with other laboratories of established quality and expertise in cholesterol determinations.

The participants can evaluate their results by comparing them with those of the National Communicable Disease Center's Medical Laboratory Branch, which is the primary reference laboratory in the program, as well as with those of two commercial laboratories of established reputation. Finally, the program makes available, without obligation or cost, the facilities of the Wisconsin State Laboratory of Hygiene on a consultation basis if a participating laboratory needs help with problems related to the determination of cholesterol by its chemistry section.

Program Structure

Samples. The study used serum samples of "known" concentrations of cholesterol. The serum pool used for each sample was analyzed by both the reference laboratories and by the participating laboratories. Two samples were distributed monthly, by mail, to each participant during the first year of the study and quarterly during the second year. (In an independent study, it was shown that serum cholesterol levels did not deteriorate during shipment of samples to the NCDC in Atlanta and back to the State laboratory, where they were analyzed a second time.)

After completing their analyses, participating laboratories sent their results to the State laboratory for computation and statistical analysis. Generally, the samples were in the normal and elevated ranges, since low-range serum specimens are difficult to obtain in sufficient quantity and, also, since the area of interest is centered on normal and elevated ranges. The results obtained were then evaluated, and monthly or quarterly reports were made to participants.

A comprehensive report, recently prepared, summarized the laboratories' 2-year results individually for their personal evaluation. Some of the information in that report is presented here.

True values. To obtain the best possible measure of the actual cholesterol content in the pooled samples, four reference laboratories of recognized quality were used to assay the samples. The samples were sent to the reference laboratories at the time the samples were mailed to the participating laboratories. By using the mean value reported by the reference laboratories, it was possible to obtain a consistent estimate of the actual cholesterol level or, as used in the context of this paper, the "true" value for the pools.

The following are the reference laboratories used in the study and their methods of analysis:

Extraction and saponification methods (*5, 6*):
Laboratory Consultation and Development Section
Laboratory Program
National Communicable Disease Center
Public Health Service
Atlanta, Ga. 30333

Biochemical Procedures
North Hollywood, Calif. 91607

AutoAnalyzer—ferric chloride method (*7*):
Special Products Division
Bio-Science Laboratories
Van Nuys, Calif. 91405

State Laboratory of Hygiene
Clinical Chemistry Section
University of Wisconsin
Madison, Wis. 53706

The State Laboratory of Hygiene was included as a reference laboratory for several reasons: (*a*) because the quality of its performance has been independently evaluated by the NCDC, (*b*) to obtain quality control data on the pools used in the study, and (*c*) to evaluate the effects of mailing samples as a regular part of the program. The samples at the State laboratory were analyzed as a part of the regular daily workload.

Results—Groups of Laboratories

Objectives. Evaluation of the results of the study by separating participating laboratories into large groups (as opposed to individual laboratories) is an attempt to consider per-

formance without inherent error due to few data or other parameters internal to individual laboratories. Grouping the laboratories by type of analysis used also allowed a comparison of the analytical methods.

For this part of the study, the participating laboratories were divided into those using direct methods and those using extraction methods. The direct methods are performed on unprocessed serum. Henry (*8*) has listed many direct methods. Also, three kits are commercially available for direct methods—the Hycel Kit (*A*), the Poly-Re-Sol Kit (*B*), and the Chole-Tech Kit (*C*). All three are used by several participating laboratories.

Table 1. Results obtained by 56 laboratories using direct methods (all values mg. per 100 cc. of blood serum)

Date	True value	Mean value	Mean error	Range	Standard deviation
1964					
December	219	228	+9	296–185	28.0
Do	290	296	+6	364–220	32.7
1965					
January	208	229	+21	302–185	26.3
Do	271	296	+25	406–249	27.6
February	194	210	+16	296–146	33.4
Do	288	290	+2	371–169	43.7
March	[1] 226	244	+18	344–156	36.0
Do	[1] 225	243	+18	334–171	31.9
April	240	244	+4	304–184	29.6
Do	285	305	+20	274–222	35.8
May	222	234	+12	285–176	29.9
Do	282	289	+7	356–238	34.0
June	206	215	+9	287–145	29.6
Do	274	285	+11	353–212	34.9
July	307	320	+13	660–249	34.5
Do	295	214	+9	358–166	24.1
August	[1] 232	260	+28	366–193	28.5
Do	[1] 225	259	+29	266–198	26.1
September	[1] 236	261	+25	458–166	27.9
Do	[1] 240	264	+24	456–166	30.0
October	240	264	+24	326–155	26.5
Do	251	278	+26	344–158	27.7
November	218	233	+15	312–193	23.1
Do	303	312	+9	459–262	30.9
1966					
February	227	235	+8	304–174	25.5
Do	293	311	+18	388–211	31.9
May	[1] 248	266	+18	381–214	21.7
Do	[1] 246	268	+18	400–210	22.8
August	250	270	+20	366–201	15.6
Do	230	252	+22	319–178	16.0
November	212	221	+9	341–118	17.0
Do	216	227	+11	324–158	16.1
Overall mean values	------	------	+15.8	--------	28.1
Standard deviation	------	------	[2] 7.4	--------	------

[1] Duplicates. The slight variation between pairs of samples indicates the precision obtained by the reference laboratories for the two samples.

[2] Standard deviation of all errors about the mean error of 16 mg. (consistency of error).

The second group of laboratories uses methods based on single or multiple extraction analyses. This group includes the laboratories using the standard procedure of Abell and associates (*5*) and those using the AutoAnalyzer (*7*) or other modified procedures (*9, 10*). The "reference method" for cholesterol determinations is generally taken to be the Abell method. The Lipid Standardization Laboratory at the NCDC, which conducts the national survey program, uses this method. According to an unpublished paper, "Variables in the Technicon N-24 Method for the Determination of Serum Cholesterol" (August 1966) by Dr. G. R. Cooper and associates at NCDC, the AutoAnalyzer method, as used by the State laboratory and others (*7*), obtains results compatible with those obtained by the Abell method.

For the purposes of evaluation of specific aspects of laboratory performance and correlation with various other parameters, the grouping of laboratories based on other criteria is discussed later.

Method of computation. For each monthly sample, the group mean is computed. This mean value is used to determine the standard deviation of the group for the particular sample. In addition, the range (smallest and largest values obtained on each sample) is also determined. The group mean is then compared to the "true" value for the sample in order to evaluate the performance of the laboratories as a group.

Interpretation. The results obtained by 56 laboratories using the direct methods are shown in table 1. The consistently high results, obtained by a comparison of the mean value of laboratories using direct methods and the true value for each sample, are due primarily to the presence of other reactive lipids in the serum (nonspecificity of the determination). The extraction methods, which increase the specificity of the determination by a separation step, eliminate most of the interfering lipids and thus give results closer to the actual cholesterol level of the serum.

The mean error of the direct methods, computed for a total of 32 samples, is +15.8 mg. per 100 cc. of blood serum with a standard deviation (scatter of the values about the mean error) of 7.4 mg. The scatter shows that the results are consistently high when compared to the true value, but they are fairly close to the mean error of 15.8 mg. The positive error (high results) is due to the nonspecific reaction with cholesterol-like substances, as previously discussed.

From the other computed data in table 1, we may interpret the large average range (highest to lowest value reported in the group) compared to the small average standard deviation as showing that most laboratories, with only a few exceptions, obtain results which agree rather closely with the mean value. In the study, it was determined that no one specific laboratory consistently occupied either the upper or lower limit of the range.

Similar data are compiled in table 2 for the 13 laboratories using extraction methods. In this case, the results agreed closely with the true value (average error of +3.6 mg. per 100 cc. of blood serum) and are scattered randomly about it. The standard deviation of the errors about their mean value was 10.8 mg. The smaller number of laboratories using extraction methods gives a less reliable estimate of the standard deviation and accounts in part for the difference from the direct methods. The fact that direct methods are less complicated and therefore less prone to experimental error may also contribute to the observed value.

Conclusions. The direct methods showed a tendency toward high results in comparison to the true value. A laboratory using a direct method, such as one of the commercial test kits, would logically expect to obtain results approximately 16 mg. higher than the actual serum cholesterol level. This fact should be considered when examining laboratory results in terms of "normal ranges," which are usually defined according to the Abell extraction method. The small standard deviation of the errors about the mean error is indicative of the precision of the direct methods.

Analysis of the data obtained in the study of the extraction methods shows that the variation about the true value is nearly random (not biased toward high or low values). The small average error (+3.6 mg.) is within the inherent variability of the method.

Results—Individual Laboratories

Objectives. The aim of the evaluation of the clinical laboratories is to assess the performance of individual laboratories in the State and also to demonstrate the advantages and value of a long-range program of independent external quality control.

To evaluate the performance of the participating laboratories, four arbitrary criteria of performance were selected. Thus, a laboratory can be evaluated with respect to all of these criteria separately or in combination. This possibility permits a more or less independent consideration of one facet of the laboratory's performance without being prejudiced by the other data.

The four evaluation criteria and the type of information obtained from each are shown in the box below.

The first three criteria represent the overall

Evaluation criteria	*Information obtained*
1. 90 percent of data reported are within ±20 mg. of mean value reported by the group of laboratories. (This criterion was chosen with very strict limits to differentiate laboratories with exceptional levels of performance.)	Measure of laboratory's ability to obtain accurate results—comparison with group mean eliminates errors due to method.
2. 90 percent of all reported data are within ±50 mg. of the mean value for the group.	Measure of the laboratory's ability to remain in control, that is, to attain consistently a "reasonable" measure of serum cholesterol.
3. Standard deviation of the laboratory's errors about its mean error is less than 25 mg.	Measure of the consistency of performance—low values indicate systematic errors, high values indicate random errors.
4. Average range of duplicate samples (analyzed at the same time) is less than 10 mg.	Measure of both precision and control of a laboratory during any given day.

performance during the study, and in effect they summarize a laboratory's performance. The fourth criterion is based on the analysis of duplicate samples and yields information regarding a laboratory's ability to reproduce its results. In all cases, no information was given to the participants as to the character of the samples (high, low, or duplicates) until the monthly report following analysis.

Table 2. Results obtained by 13 laboratories using extraction methods (all values mg. per 100 cc. of blood serum)

Date	True value	Mean value	Mean error	Range	Standard deviation
1964					
December	219	234	+15	298–207	31.5
Do	290	308	+18	378–250	31.7
1965					
January	208	228	+20	306–181	44.6
Do	271	295	+24	358–250	38.8
February	194	207	+11	264–176	29.8
Do	288	292	+4	370–230	45.6
March	[1] 226	228	+2	273–195	27.5
Do	[1] 225	225	0	266–185	28.1
April	240	256	+16	360–205	52.7
Do	285	295	+10	345–259	35.4
May	222	233	+11	302–197	34.2
Do	282	282	0	310–260	16.3
June	205	206	−1	340–187	18.6
Do	274	271	−3	460–240	23.6
July	205	211	+6	251–176	24.0
Do	307	311	+4	358–280	29.1
August	[1] 232	228	−4	252–194	18.9
Do	[1] 225	235	+10	262–192	24.4
September	[1] 236	232	−4	260–175	29.5
Do	[1] 240	234	−6	260–185	29.5
October	240	227	−13	272–162	42.1
Do	251	233	−18	284–175	42.3
November	218	216	−2	238–198	16.3
Do	303	280	−23	312–254	20.3
1966					
February	227	218	−5	245–190	20.1
Do	293	282	−11	305–248	22.2
May	[1] 248	257	+9	274–209	23.8
Do	[1] 246	256	+10	366–201	15.6
August	250	259	+9	280–241	13.9
Do	230	239	+9	254–221	11.0
November	212	221	+9	238–152	9.4
Do	216	225	+9	238–164	9.1
Overall mean values	------	------	+3.6	--------	26.5
Standard deviation	------	------	[2] 10.8	--------	------

[1] Duplicates. The slight variation between pairs of samples indicates the precision obtained by the reference laboratories for the two samples.

[2] Standard deviation of all errors about the mean error of 3.6 mg. (consistency of error).

Method of evaluation. To determine the performance of the laboratory with regard to the criteria chosen, each laboratory was considered individually. Its results on the sample were evaluated according to the various criteria.

Evaluation of reference laboratories. The evaluation criteria, plus both algebraic and absolute summations of deviations from mean values, show the performance of the reference laboratories (table 3). Since all the reference laboratories meet acceptable limits on all of the criteria, actual numerical data are shown instead of the "acceptable" or "not acceptable" designations used elsewhere. The data in table 3 are, of course, internally biased since the four reference laboratories are compared only with each other. These results are of value, however, in that the information provides an independent check on the acceptability of the criteria for evaluation, and the data can be used to compare the consistency of the performance of the reference laboratories.

Of the two additional criteria, the average absolute error is computed from a summation of the absolute values of the errors on individual samples from the true value and is a measure of the closeness to the true value routinely obtained by the laboratory. The algebraic error, on the other hand, is also based on a similar summation, but taken with regard to sign, and is an indication of the consistency of the results. In either case, the very low values obtained by the reference laboratories show their errors to be both random and small.

Evaluation of participating laboratories. On the basis of the previously described criteria, the participants are evaluated by comparing their results to the mean values achieved by their group. A primary evaluation based on laboratory success in fulfilling the various criteria shows the following: laboratories achieving four acceptable criteria, 9 percent; three acceptable, 38 percent; two acceptable, 28 percent; one acceptable criterion, 16 percent; no acceptable criteria, 10 percent. In view of the relative "strictness" of criterion 1, the low percentage is important only in that it indicates those laboratories which consistently perform on an exceptional level. Three or more acceptable criteria,

obtained by 47 percent of participants, is a more accurate indication of good overall performance.

On the other hand, 26 percent of the laboratories fulfilled either one or none of the criteria and thus, by the criteria chosen for this study, were not performing at acceptable levels. The data reported here, however, represent only the first 2 years of the program, and some of these laboratories have shown subsequent improvement. The continuing study and evaluation will probably reveal further improvements, as well as more statistically valid conclusions.

Other types of information may be ascertained from the accumulated data. In the following list, the participating laboratories are grouped by other arbitrarily chosen common factors.

Group 1: All laboratories
Group 2: Laboratories using direct methods, including all kits
Group 3: Laboratories using extraction methods, including AutoAnalyzer
Group 4: Laboratories headed by a person holding a doctorate (M.D., Ph.D., pathologist)
Group 5: Laboratories using commercial kits
Group 6: Large laboratories (workload of more than 20 samples per week)
Group 7: Small laboratories

Table 4 shows the data on fulfillment of the various criteria by the seven groups listed. This table is an attempt to answer colleagues' questions as to the factors which may affect the laboratory performance.

The most valid evaluation of the data in table 4 is a comparison of the individual groups with the participants as a whole (group 1). The various groups should be compared on the basis of a "good" performance (acceptable on three or four criteria), "fair" but needing improvement (acceptable on two criteria), and "unacceptable" performance (acceptable on none or one of the criteria). The overall consensus (group 1) showed three-fourths of the laboratories in the "extreme" categories—47 percent in the "good" and 26 percent in the "unacceptable."

On this basis, data for the direct (group 2) and extraction (group 3) laboratories show no significant differences from the group 1 data. Likewise, the laboratories headed by persons holding a doctorate, about 60 percent of the total (group 4), show little variation from the entire group.

The laboratories using a commercial kit method (group 5) show a slightly different spread of data, with a more even distribution among the five criteria. Interestingly, all six

Table 4. Data on fulfillment of criteria by laboratories in various groups

Group	Number of laboratories	Percentage of group				
		4 criteria	3 criteria	2 criteria	1 criterion	0 criterion
1	69	9	38	28	16	10
2	56	11	34	30	14	11
3	13	0	54	15	23	8
4	46	9	37	33	11	11
5	51	12	29	33	18	8
6	19	16	53	16	16	0
7	49	6	33	31	16	14

Table 3. Evaluation of reference laboratories

Laboratory	Evaluation criteria [1]				Algebraic average error (mg.)	Absolute average error (mg.)
	1 (percent)	2 (percent)	3 (mg.)	4 (mg.)		
National Communicable Disease Center	95	100	7.5	9.0	−1	5.0
Bio-Science Laboratories	97	90	6.0	3.0	+1	5.0
Biochemical Procedures	93	100	10.8	6.0	+1	6.0
Wisconsin State Laboratory of Hygiene	100	100	7.4	4.0	0	6.0
Acceptable range	>90	>90	<24	<10	----------	----------

[1] The evaluation criteria are described on p. 960.

laboratories which achieved a perfect "4 of 4" on the evaluation criteria are in the group using commercial kits. Curious also is the fact that four of the six laboratories in the "0 of 4" category also use the commercial kits. This result seems to indicate that results obtained with the kits reflect (as do all chemical testing procedures) the skill and care of the persons or laboratories performing the analysis.

Finally, on the basis of "large-small" (groups 6 and 7) laboratory workloads, the larger laboratories attained a greater percentage in the "good" category. This observation could reflect a number of variables, such as specialization among laboratory personnel, internal quality control, or more elaborate equipment. The laboratories with a smaller workload showed a slightly lower percentage in the "good" category, but this group contained three of the six laboratories in the "4 of 4" category. This record indicates that a large workload is not a prerequisite for achieving good results and shows the value of external quality control in providing an unbiased evaluation of performance.

Discussion

This report does not show short-term improvement in the participants' performance, which, it is hoped, is a logical outgrowth of cooperation in an external quality control program. Our redesigned, continuing program based on computer-analyzed reporting does incorporate this feature.

The success or failure of this or any program of quality control is difficult to quantitate. However, the fact that a laboratory becomes aware of the importance of quality control is a notable success in itself. The laboratories under responsible direction profit most from this type of program, in which an unbiased external evaluation of performance provides the director with important information, which is needed for critical appraisal of laboratory performance.

The data in this paper are also internally biased because the program is voluntary. The participating laboratories had a sincere interest in external quality control at the outset and consequently made the overt effort to join this program. Logically, their performance might be expected to already reflect their awareness of the need and value of a program of quality control.

Summary

The State of Wisconsin is conducting an external quality control program to evaluate cholesterol determinations among clinical laboratories. The laboratories are participating voluntarily, and they include a cross section of types—hospital, clinic, group practice, individual physicians' offices, and independent laboratories.

The results obtained during the first 2 years of the program, 1964–66, by 69 laboratories were evaluated in two ways: (*a*) by their method of analysis (direct or extraction) and (*b*) by laboratory groups, according to size of workload, use of commercial kits, directors' training, and other factors.

Laboratories using direct methods of analysis showed elevated results, while the results of those using extraction methods correlated more closely with actual cholesterol levels. Generally, by the criteria chosen for evaluation, one-half of the participants performed at acceptable levels, one-fourth at the middle level, and one-fourth at unacceptable levels.

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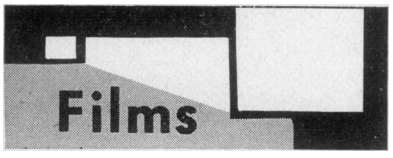
EQUIPMENT REFERENCES

(A) Hycel Cholesterol Kit: Hycel, Inc., Houston, Tex. 77039.
(B) Poly-Re-Sol Kit: Hoppers Laboratories, Inc., Fredericksburg, Tex.
(C) Chole-Tech Kit: Uni-Tech Chemical Manufacturing Co., Sun Valley, Calif. 91353.



To Face Life Again: Rehabilitation through reconstructive plastic surgery. *Motion picture, 16 mm., black and white, sound, 28 minutes, 1966; order No. AM–1397. Produced by the Society for the Rehabilitation of the Facially Disfigured, Inc., with the aid of a grant from the Vocational Rehabilitation Administration, Department of Health, Education, and Welfare.*

AUDIENCE: Nurses, nursing assistants, medical social workers, rehabilitation counselors, physiatrists, physical therapists, occupational therapists, and allied personnel.

SUMMARY: Illustrates various types of facial disfigurement and hand disorders caused by disease such as cancer, trauma, and congenital defects. Describes the basic problem, demonstrates surgical methods of rehabilitation, and shows in interviews the adjustment of patients to their conditions.

AVAILABLE: Free short-term loan from Public Health Service Audiovisual Facility, Atlanta, Ga. 30333, Attention: Distribution Unit. Purchase from DuArt Film Laboratories, Inc., 245 West 55th Street, New York, N.Y. 10019.

Histoplasmosis, Mason City, Iowa. *Motion picture, 16 mm., color, sound, 16 minutes, 1966; order No. M–1228. Produced by the Public Health Service Audiovisual Facility, for the National Communicable Disease Center, Atlanta, Ga.*

AUDIENCE: Personnel of State and local health organizations, medical schools and teaching hospitals, universities and institutions offering courses in mycology, and of the U.S. Fish and Wildlife Service.

SUMMARY: Describes two outbreaks of histoplasmosis in Mason City, Iowa, and illustrates how the source was decontaminated as a control measure. The film begins with a description of the clinical symptoms of histoplasmosis and the route of infection, followed by an account of the epidemiologic investigation of the two outbreaks. The latter part of the film illustrates how the source was decontaminated as a control measure after the second outbreak, by spraying the 5-acre site with a 3 percent formalin solution.

AVAILABLE: Free short-term loan from Public Health Service Audiovisual Facility, Atlanta, Ga. 30333, Attention: Distribution Unit. Purchase from DuArt Film Laboratories, Inc., 245 West 55th Street, New York, N.Y. 10019.

The Coming Crisis in Veterinary Medicine—Are You Prepared? *Television film recording, 16 mm., black and white, sound, 30 minutes, December 1966; order No. TFR–1292. Produced by the Public Health Service Audiovisual Facility.*

AUDIENCE: Veterinarians and allied biomedical personnel.

SUMMARY: Presents a speech by Jacob Antelyes, D.V.M., Middle Village, N.Y., delivered at a general session of the 103d Annual Meeting of the American Veterinary Medical Association in Louisville, Ky., July 13, 1966. Advocates increased efforts on the part of every veterinarian in mankind's battle against disease, ignorance, and poverty. Emphasizes the need for global concern about food shortages and health manpower and makes a plea for greater attention from the professional man in all of these fields.

AVAILABLE: Free short-term loan from Public Health Service Audiovisual Facility, Atlanta, Ga. 30333, Attention: Distribution Unit. Not presently available for purchase.