Diabetes Detection with a Comparison of Screening Methods

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SUMMARY

During a Diabetes Detection Drive, 559 persons were tested for hyperglycemia (AutoAnalyzer and Dextrostix methods) or glycosuria (Clinistix and Dreypak methods) ninety minutes after a glucose load. Of 164 screened positive, 154 returned for standard glucose tolerance testing. Using the criteria of Fajans and Conn, forty-two new cases of diabetes were diagnosed; by age-adjusted criteria there were twenty new cases. Approximately one-third of these would have been missed by reliance on screening by glycosuria alone. Comparison of screening methods reveals the AutoAnalyzer measurement of blood sugar to be more sensitive and therefore better for the intensive study of limited populations; however, the Dextrostix method is cheaper and quicker and may have some advantages in the usual mass detection efforts. DIABETES *20*:109-16, February, 1971.

A successful Diabetes Detection Drive should not only uncover a sufficient number of new diabetics but also should prove educational to the medical community, and be a rewarding enterprise for participating lay workers. Achievement of these goals requires careful planning for the best use of available resources and facilities. Of particular importance is the selection of a screening method which is simple and inexpensive on the one hand, yet sensitive and specific on the other, and still flexible enough to accommodate any unexpected deficit or surplus of screenees. Most workers in the field agree on the need for a glucose challenge for enhanced sensitivity in testing, but few would insist on screening with the precision of a quantitative blood sugar if a simpler yet satisfactory substitute were available.

During a recent detection drive we compared four screening methods in terms of sensitivity and specificity, as verified by subsequent standard glucose tolerance tests. Despite the limited scope of the study, the information gained may be helpful in planning for comparable community detection efforts.

METHODS AND MATERIALS

Following a well-publicized campaign in preparation for National Diabetes Week, 1968, the Diabetes Detection Drive was held in the University of Virginia Hospital. Following registration, each person underwent measurement of height and weight, emptied his bladder, and then ingested the equivalent of 75 grams of glucose in the form of a mixture of monosaccharides and disaccharides (Glucola, Ames).[1] The subjects remained in the area, consuming no foods or liquids other than water. One and one-half hours later, venous blood was collected; a generous drop was spread on a Dextrostix (Ames) Strip and the color change noted after sixty seconds. The rest of the blood was transferred to a Vacutainer tube (EDTA-fluoride, Becton-Dickinson), and plasma glucose was determined by the AutoAnalyzer ferricyanide (Hoffman) method. Promptly thereafter, a urine collection was obtained and immediately tested for glucose with Clinistix (Ames) test strips. (If results were positive, reducing substances were measured quantitatively by the Benedict method.) In addition, a Dreypak strip was dipped into the urine, allowed to dry, and tested four days later (the usual time lapse associated with the home testing, mail-in method).

During the Diabetes Detection Drive, 559 subjects were screened. If either of the urine tests revealed glycosuria, if the AutoAnalyzer value was 155 mg./100 ml. or greater, or if the Dextrostix was read as 135 mg./100 ml. or greater, the subjects were recalled for further testing; 164 subjects fulfilled these criteria. Seven

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were known diabetics (confirmed by their personal physicians), however, and therefore excluded, two moved from the area, and one refused to return. As a result, 154 were retested.

The 154 subjects were asked to consume a 300 gram carbohydrate diet for three days prior to the glucose tolerance test, and to take only water after midnight prior to the test. Glucose tolerance tests were begun between 8:15 a.m. and 8:45 a.m., employing Glucola, which was ingested within a five minute period. The patients remained in the test area throughout the period. Blood was collected at fasting, and at one-half hour, one hour, one and one-half hours, and two hours after Glucola ingestion. All plasma samples were analyzed for glucose by the AutoAnalyzer method within three hours.

The criteria for diagnosis of diabetes were those of Fajans and Conn,[2] arbitrarily corrected for the use of plasma instead of blood, viz. values in excess of 185 mg./100 ml. at one hour, 160 mg./100 ml. at one and one-half hours, and 140 mg./100 ml. at two hours. Test results which exceeded these levels at one or two but not all hours were called indeterminate. For the sake of comparison, the diabetic group was subdivided into those who were or were not diabetic using age-adjusted criteria. As previously described,[3] these are derived from the Tecumseh population study of Hayner et al.,[4] and involve raising the plasma glucose values required for the diagnosis of diabetes: 15 mg./100 ml. at one hour, 12.5 mg./100 ml. at one and one-half hours, and 11.5 mg./100 ml. at two hours, for every decade of age above 20.

The hypotheses to be tested were: (1) glycosuria of any degree would screen as efficiently as hyperglycemia using the Fajans and Conn criteria for the diagnosis of diabetes; and/or (2) glycosuria of any degree would screen as efficiently as hyperglycemia using the age-adjusted criteria for the diagnosis of diabetes; and (3) both blood glucose methods would be equally efficient in screening. The new cases of diabetes have been cate-

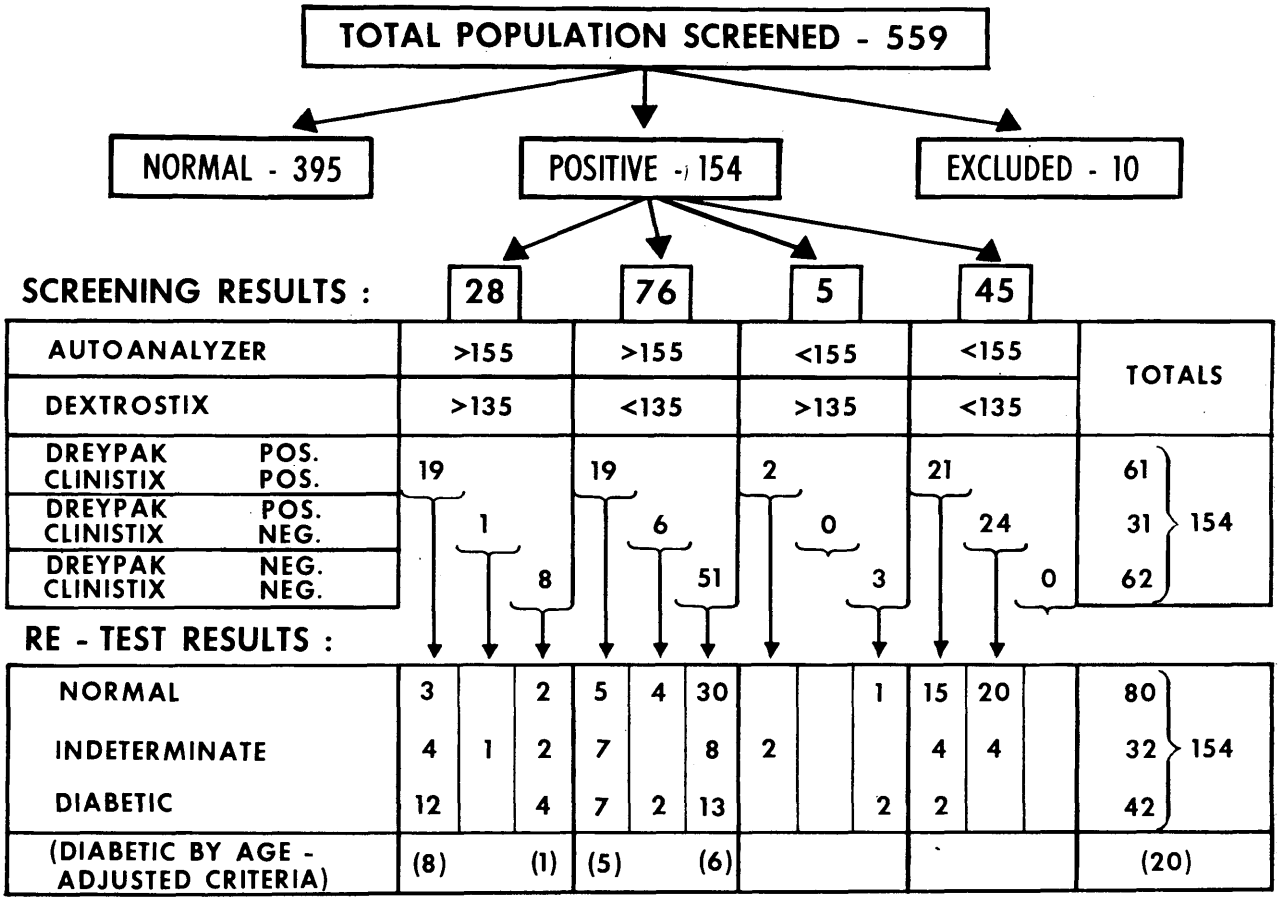


FIGURE 1

gorized in terms of their response to initial screening tests and the differences analyzed by reference to a table of binomial population percentages.[5]

Finally, the sensitivity and specificity of screening at different levels of blood glucose are compared for the two methods used.[6]

RESULTS

The results of screening and retesting are diagrammed in figure 1. Using the criteria of Fajans and Conn, we discovered forty-two new diabetics, or seventy-six per 1,000 screened; by age-adjusted criteria these figures are twenty, or thirty-six per 1000, respectively. These values are higher than the twenty-thirty per 1000 usually reported, perhaps reflecting the intensive retesting effort.

We were forced to classify thirty-two of the 154 glucose tolerance tests (21 per cent) as indeterminate, using the definition previously given. These individuals were not tested further but were advised to participate in future Detection Drives and/or to consult their physicians periodically for repeated testing. The variability of mild abnormalities in glucose tolerance on repeated testing is well known.[7]

The findings are recast in table 1, with an extensive breakdown by age and sex. We have no data on occupation. Several general impressions are gained from study of the table, although the numbers involved are too few to justify any conclusions. First, the median age of the screenees was in the high forties, and women outnumbered men 7:4. Second, the prevalence of diabetes increased progressively from the fourth through the eighth decade; use of age-adjusted criteria minimized this increase through the seventh decade, but not in the eighth. Finally, and very tentatively, men seemed more likely to demonstrate nonhyperglycemic glycosuria than women, while the converse sex difference seemed to hold true for nonglycosuric hyperglycemia.

Although thirty-one subjects had glycosuria detected by Dreypak but not by Clinistix, the converse never occurred. Of these thirty-one, twenty-four had only the Dreypak test (no hyperglycemia) as a positive screen; none of these were shown to be diabetic. The Clinistix method detected glycosuria in true diabetics in concentrations as low as 0.17 per cent, and glycosuria in nondiabetics in concentrations as high as 2.5 per cent. The Dreypak test behaved similarly, but in general the correlation between its color changes and quantitative glycosuria was loose and unpredictable. Finally, nineteen subjects without any screening glycosuria were later shown to be diabetic.

TABLE 1

Results of Diabetes Detection Drive by age and sex (M, F)

Decade of Age		11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90	TOTAL
Number Screened		19 (5, 14)	84 (41, 43)	83 (31, 52)	121 (39, 82)	115 (41, 74)	90 (28, 62)	44 (14, 30)	3 (2,1)	559 (201, 358)
Positive Screen by	Blood only		1 (1, 0)	6 (0, 6)	11 (2, 9)	14* (4, 10)	19 (3, 16)	13* (3, 10)		64* (13, 51)
	Urine only	3 (1, 2)	9 (4, 5)	6* (4, 2)	9 (4, 5)	9 (6, 3)	7* (4, 3)	4 (4, 0)		47* (27, 20)
	Blood + Urine			6* (2, 4)	16 (8, 8)	10* (5, 5)	10* (3, 7)	10* (5, 5)	1 (1,0)	53* (24, 29)
Diabetic by F & C, not A.A. Criteria	Total	0	0	1 (1, 0)	2 (0, 2)	5 (2, 3)	9 (0, 9)	5 (2, 3)	0	22 (5, 17)
	per 1000 Screened	—	—	12 (33, 0)	17 (0, 24)	43 (49, 41)	100 (0, 150)	114 (146, 100)	—	39 (25, 48)
Diabetic by Age-Adjusted Criteria	Total	0	0	2 (0, 2)	4 (3, 1)	5 (4, 1)	4 (1, 3)	4 (1,3)	1 (1, 0)	20 (10, 10)
	per 1000 Screened	—	—	24 (0, 38)	30 (77,12)	41 (97, 35)	44 (36, 48)	91 (72, 100)	—	36 (50, 28)
All Diabetics	Total	0	0	3 (1, 2)	6 (3, 3)	10 (6, 4)	13 (1, 12)	9 (3, 6)	1 (1, 0)	42 (15, 27)
	per 1000 Screened	—	—	36 (32,38)	50 (77, 12)	87 (150, 54)	145 (36, 194)	205 (214, 200)	—	75 (75, 76)

* Includes known diabetics, who do not appear elsewhere in this table.

On the other hand, the blood tests were clearly more valuable as predicters of diabetes. The AutoAnalyzer screening level (plasma glucose of 155 mg./100 ml. or greater) was exceeded in 104 subjects, including thirty-eight of the forty-two eventually determined to be diabetic. The Dextrostix screening level (blood glucose of 135 mg./100 ml. or greater) was exceeded only thirty-three times, finding eighteen (but missing twenty-four) of the forty-two eventual diabetics.

If these forty-two subjects are categorized in terms of their initial response, it is clear that half were screened positive by some combination of hyperglycemia and glycosuria. Of the remaining twenty-one, nineteen were screened positive by hyperglycemia without glycosuria and only two by glycosuria without hyperglycemia. If these twenty-one subjects were a strictly random sample from a very large population of diabetics in whom the test differed in their verdicts, the estimated upper limit of the population frequency of true diabetics with glycosuria but no hyperglycemia would be 31 per cent (maximum frequency of underestimation = 2.5 per cent of all such estimates). Therefore it seems highly unlikely that screening by glycosuria actually detects diabetes as often as screening by hyperglycemia, under the conditions of this study.[5] Accordingly, no evidence is found to support the first hypothesis. The corresponding estimated upper limit of frequency is 41 per cent when based on the twenty subjects considered diabetic by age-adjusted criteria. (Seven had nonglycosuric hyperglycemia, while none had nonhyperglycemic glycosuria.) Thus, evidence to support the second hypothesis is not available either.

Since whole blood with a glucose concentration of 135 mg./100 ml. will contain a plasma glucose concentration of about 155 mg./100 ml., the two blood screening methods were planned to be strictly comparable. Therefore, there should be no difference in their efficiency as screening tests for diabetes. However, twenty-four of the forty-two had a discrepancy in terms of original blood sugar screening: twenty-two had AutoAnalyzer values over 155 mg./100 ml.; but Dextrostix values under 135 mg./100 ml.; the converse was true in two cases. Again, if these twenty-four were a random sample of a population of true diabetics whose screening tests differed this way, the estimated upper limit of the population frequency of true diabetics screened positive by Dextrostix but not by AutoAnalyzer hyperglycemia would be 27 per cent (maximum frequency of underestimation = 2.5 per cent, as above).[5] Finally, even if the comparison is limited to the eleven age-adjusted diabetics with discrepancy in their screening results (all eleven positive by AutoAnalyzer but not by Dextrostix), the corresponding estimated upper limit of frequency is only 29 per cent. Thus Dextrostix screening seems quite unlikely to discover diabetics as often as AutoAnalyzer screening, at the levels chosen, and therefore the third hypothesis cannot be substantiated.

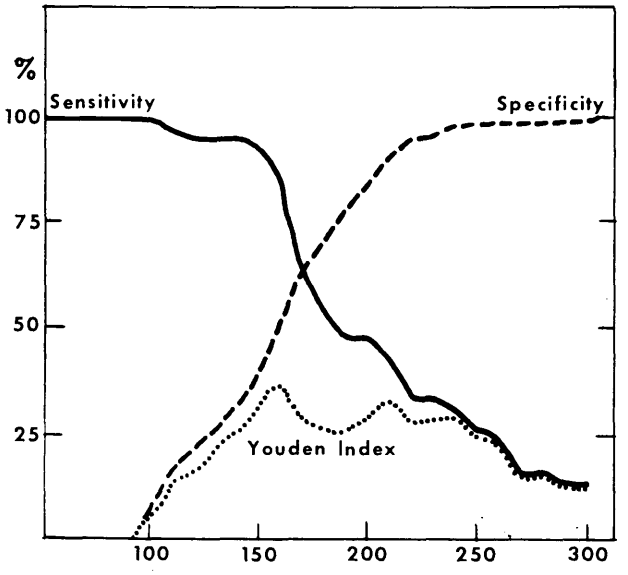
This puzzling discrepancy might be spurious. Through error, the Dextrostix screening level might have been set too high, the AutoAnalyzer level too low, or both. Therefore it seemed imperative to compare both methods in terms of sensitivity and specificity, which depend upon a calculation of the number of true or false (i.e., later confirmed or disproved) screened positive or negative at any given screening level. Sensitivity is defined as the percentage of all diabetic subjects which gives a positive screen at that level (= true positives × 100/all diabetic), while specificity is the percentage of all nondiabetic subjects which gives a negative screen at that level (= true negatives × 100/all nondiabetic). The Youden Index, sometimes useful, is sensitivity + specificity − 100.

Since every subject provides concurrent AutoAnalyzer and Dextrostix readings for blood sugar, these calculations are easily carried out—but only if three assumptions can be made. The first is that follow-up of all positive screenees was complete: 154 of 157 (98 per cent) were retested, which seems acceptable.

Second, for proper calculation of sensitivity and specificity all 559 subjects (less the seven known diabetics) should have been retested. But for practical reasons this was not possible, so no one with AutoAnalyzer plasma glucose below 155 mg./100 ml. and Dextrostix blood glucose below 135 mg./100 ml. and aglycosuria was retested. The assumption is that no one of these 395 individuals would have been diagnosed as diabetic if retested appropriately, and this is probably false. But the number of such missed diabetics is probably small and, if included, would not alter the calculations charted in figures 2 and 3; the effect would be to shift the sensitivity line downward, and the crossover point to the left, thereby slightly lowering the Youden Index to a similar extent for both AutoAnalyzer and Dextrostix data.

Finally, it is assumed that a complete glucose tolerance test, one to five months after screening, is accurate final proof of permanent diabetes. There is considerable evidence against this; indeed, glucose tolerance tests repeated in the same individual often vary over a period of time.[3,7] But in the usual follow-up of Diabetes Detection Drives, the glucose tolerance test is always rec-

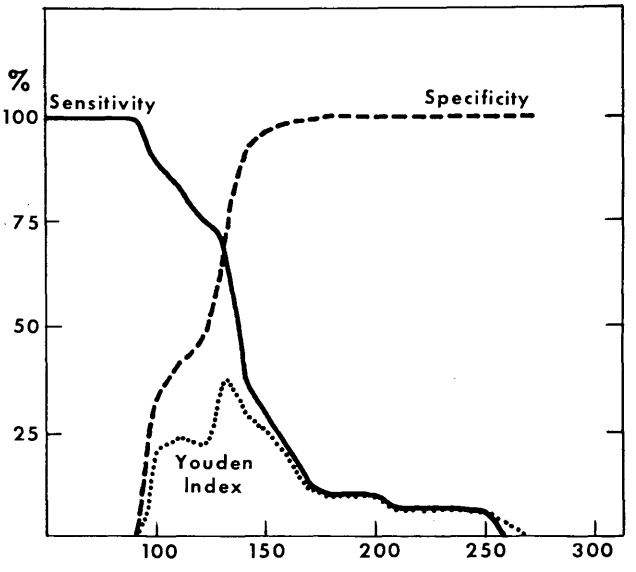
SENSITIVITY, SPECIFICITY AND YOUDEN INDEX FOR AUTOANALYZER SCREENING



AUTOANALYZER BLOOD SUGARS (mg. per 100 ml.)

FIGURE 2

SENSITIVITY, SPECIFICITY AND YOUDEN INDEX FOR DEXTROSTIX SCREENING



DEXTROSTIX BLOOD SUGARS (mg. per 100 ml.)

FIGURE 3

ommended as the standard of good clinical practice.

If these assumptions are acceptable, the sensitivity and specificity curves shown in figures 2 and 3 provide an answer to the apparent discrepancy between Auto-Analyzer and Dextrostix screening. The crossover point and maximum Youden Index value occurs at a Dextrostix blood glucose of 130 mg./100 ml.; the Auto-Analyzer curve shows the same maximum Youden Index (37) at a plasma glucose of 160 mg./100 ml. We suspect our low yield from Dextrostix screening at 135 mg./100 ml. may represent a systematic observer error in reading the color strips. If one takes the position that sensitivity and specificity are considered equally important considerations in the choice of screening methods, it would seem that there is no longer any reason to prefer the AutoAnalyzer screening plasma glucose of 160 mg./100 ml. to the Dextrostix screening blood glucose of 130 mg./100 ml.

Yet many authorities would deny that sensitivity and specificity are equally important. For these, there is some comfort in the formula proposed by Blumberg,[8] who has assigned weighted values to true positive, true negative, false positive and false negative screening results so as to calculate a meaningful, realistic V_L—the health value to the community of screening for diabetes at a given level L. His formula is $V_L = V_{TP}\ TP_L + V_{TN}\ TN_L + V_{FP}\ FP_L + V_{FN}\ FN_L$, where

V_{TP} = health value to the community of one true positive,

V_{TN} = health value to the community of one true negative,

V_{FP} = health value to the community of one false positive,

V_{FN} = health value to the community of one false negative,

TP_L = number of true positives resulting from screening at level L,

TN_L = number of true negatives resulting from screening at level L,

FP_L = number of false positives resulting from screening at level L,

FN_L = number of false negatives resulting from screening at level L.

Assignment of numerical values for these categories is bound to be controversial, but Blumberg's calculations show that the peak is sharper when the disadvantage of a false positive screen is judged less troublesome than that of a false negative screen. Since this is the popular feeling about diabetes detection, the arbitrary values used in this comparison will be those preferred by Blumberg, i.e. $V_L = 10\,TP_L + 0\,TN_L - 2\,FP_L - 5\,FN_L$. While some may challenge the assignment of

these specific weights, any set is sufficient to serve as a means of comparing two screening methods used in the same population.

The calculations of V_L for any screening value permit the construction of the curves shown in figure 4, comparing the peak obtained with the AutoAnalyzer results to that provided by the Dextrostix results. The lines to the right of the peak reflect data obtained from the 154 subjects who were retested; their dotted extensions to the left of the peak are calculated with the assumption that there were no cases of undiscovered diabetes among the 395 who were not retested; rare exceptions, if present, would alter this curve very little. The AutoAnalyzer curve has a higher peak, $V_L = 220$ for a plasma screening level of 160 mg./100 ml., while the Dextrostix curve peaks with a maximum $V_L = 146$ for a whole blood screening value of 130 mg./100 ml. In other words, to the extent that the discovery of all true positives is the overriding consideration, a high sensitivity becomes critical no matter how low the specificity.

DISCUSSION

A few general comments seem appropriate. The use of Glucola as a carbohydrate load was based on considerable prior experience of others as well as ourselves.[1,3,9-11] We have always obtained blood samples at ninety minutes, an interval that seems to combine practicality with dependability.[3,10] Because we have always used the criteria of Fajans and Conn for normal glucose tolerance, it seemed appropriate to use their upper-limit-of-normal value (whole blood sugar of 135 mg./100 ml. by Somogyi-Nelson method) for ninety minutes as a screening level for diabetes. The transformation to a plasma glucose value of 155 mg./100 ml. by the AutoAnalyzer method was made by adding 15 per cent. Finally, the age-adjusted criteria were derived from the well-known Tecumseh, Michigan, population study of Hayner et al.[4] These authors found that age was associated with a progressive upward trend of 1-hour post-challenge whole blood sugar values, averaging 13 mg./100 ml. per decade over twenty years. Assuming proportional elevations for the 1½-hour and 2-hour values, the Fajans and Conn criteria would remain (respectively) 160, 140, and 120 mg./100 ml. for age twenty, but would be 173, 151, and 130 mg./100 ml. for age thirty and 186, 162, and 140 mg./100 ml. for age forty, etc. These minimal values for the diagnosis of diabetes were of course converted to their plasma equivalents in interpreting our data.

The technological advances which made blood chemistry speedy and efficient have revealed the deficiencies of screening populations for diabetes by means of urine testing alone. The studies of Osserman and Starin,[12] Stewart and Robertson,[13] and Jackson et al.[14] demonstrated that roughly one-third of those with eventually proven diabetes do not have glycosuria after a glucose load. The present study can only confirm this insensitivity, without necessarily concurring in the obituary, as will be seen.

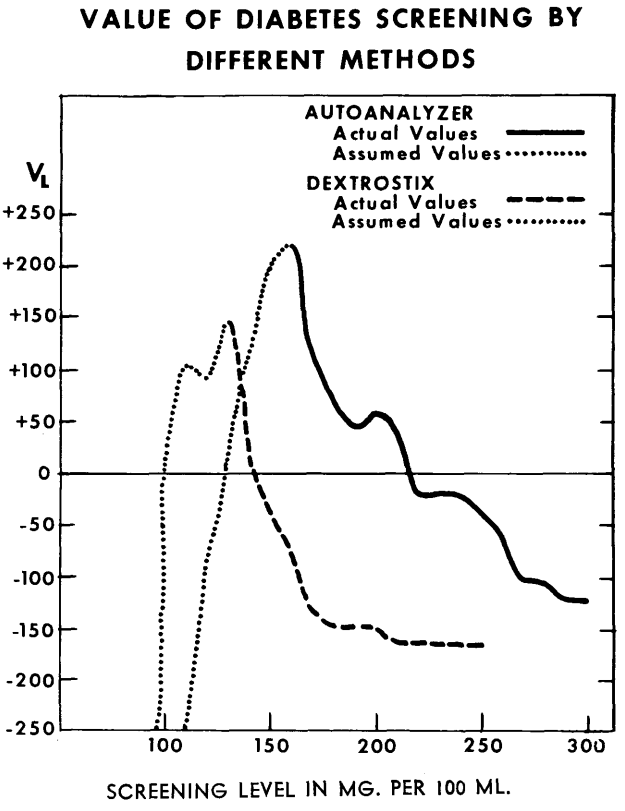


FIGURE 4

If hyperglycemia is the best screening clue to diabetes, the blood glucose method becomes critical. The Dextrostix method has been previously used in mass screening by a number of investigators[9,15,16] who commented favorably on its over-all performance in comparison with more precise analytical methods. Under the conditions of our study, even in the hands of inexperienced personnel, it achieved sensitivity and specificity values which give a Youden Index value identical to that for the AutoAnalyzer method. On the other hand, the comparison by means of Blumberg's formula reinforces our scientific bias in favor of complete, or near-complete, recovery of all undiscovered diabetics in the population screened, and therefore favors Auto-

Analyzer blood glucose.

This dilemma solves itself when viewed in perspective of the over-all problems of diabetes detection. If resources are relatively unlimited, if the population to be screened is relatively finite, and if good follow-up is assured, the AutoAnalyzer screening is obviously preferable. However, our usual experience has been with a different situation: limited funds, personnel and space for a drive, a large, relatively unlimited population readily attracted by appropriate publicity, and considerable problems with follow-up unless screenees can be promptly notified. In such a situation the Dextrostix method works well because positive screenees can be detected on the spot, and appointments made for their follow-up before they leave the building. This saves much secretarial effort, paperwork, and postage, and cooperation in the follow-up is vastly better.

If in this situation one wishes to calculate how to find the largest number of diabetics with limited funds (regardless of how many diabetics are missed), he might assemble the pertinent information and work out a formula like that shown below. (The upper case letters refer to specific values worked out at the time for any given situation. The lower case letters are those derived from the present study of this specific population; they may not be applicable to other populations at other times in other places.) Let

L = cost of a single loading dose of carbohydrate (Glucola or its counterparts, lemon-flavored dextrose, Karo, etc.) calculated to include container, flavoring, preparation time, etc.

S = cost of a single laboratory screening method (blood or urine) including equipment, handling, personnel costs, etc.

G = cost of a repeat glucose tolerance test, including secretarial and postage cost of notifying positive screenees. (If these are referred to private physicians, the secretarial costs increase but laboratory costs, to the D.D.D., are nil.)

F = amount of funds or counterpart contributions available.

X = number of individuals screened.

R or (r) = percentage of screenees with positive results, using a given screening method.

D or (d) = percentage of positive screenees eventually diagnosed as diabetic, using a given screening method.

Using this formula, the cost of the D.D.D. will be: $\text{Cost} = X(L + S) + XRG$. Since the cost should not exceed the resources available, the number of screenees admitted can be calculated in advance: $X = \frac{\text{Cost}}{L + S + RG}$. Similarly, the number of new diabetics detectable in this number of screenees can be calculated as XRD and predicted (very roughly, of course) by using the factors r and d calculated from the present study, as shown in table 2. For example, if one dose of Glucola (L) costs \$1, an AutoAnalyzer plasma glucose (S) \$2, and a complete glucose tolerance (G) \$7, then for \$1,000 one can screen (by AutoAnalyzer plasma glucose of 160 mg./100 ml.) $\frac{\$1{,}000}{\$1 + \$2 + .174 \times \$7}$ or $\frac{\$1{,}000}{\$3.00 + \$1.218}$ or 238 individuals, a population yielding $238 \times .064$ or fifteen new diabetics. However, using the Dextrostix method at \$0.39 per determination, one can screen (by Dextrostix blood glucose of 130 mg./100 ml.) $\frac{\$1{,}000}{\$1 + \$0.39 + .159 \times \$7}$ or $\frac{\$1{,}000}{\$1.39 + \$1.12}$ or $\frac{\$1{,}000}{\$2.51}$ or 400 individuals, and can expect to find $400 \times .054$ or twenty-two new diabetics for the same expenditure of \$1,000. Similar calculations can be worked out for the urine testing methods or for combinations of blood and urine testing. It cannot be too strongly reemphasized that L, S, G and F must be practical and realistic figures and that our values for r and d may not be applicable elsewhere.

Even with this disclaimer, we hope the above formula may be useful to the organizers of future Diabetes Detection Drives. If its use is based on a sound appraisal of the resources at hand, it should make possible the selection of an appropriate screening method, indicate the financial limitation on the number of screenees, and

TABLE 2

Formula values derived from study of present population of 559 screenees (percentages expressed as decimals)

Factor	Screening Test Used				
	Auto-Analyzer plasma glucose > 160 mg./100 ml.	Dextro-stix blood glucose > 130 mg./100 ml.	Clini-stix positive	Dreypak positive	Dextro-stix > 130 mg./100 ml. + Clini-stix positive
r	.174	.159	.109	.164	.210
d	.367	.340	.349	.292	.290
rd	.064	.054	.038	.048	.061
d'*	.196	.157	.213	.141	.146
rd'*	.034	.025	.024	.023	.031

* d' factor indicates fraction of positive screenees who are eventually diagnosed as diabetic by age-adjusted criteria.

even suggest the approximate number of new diabetics to be diagnosed. And the ability to make such a forecast, even if only partially correct, is after all one of the great desiderata of a successful Diabetes Detection Drive.

ACKNOWLEDGMENT

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