

Epidemiologic Findings on the Relationship of Time of Day and Time Since Last Meal to Glucose Tolerance

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SUMMARY

Data from 10,559 men and women, age 30-64, participating in the morning and afternoon in a Chicago Health Department multiphasic screening project, were used to determine the effects of time of day and time since last meal on the values for plasma glucose one and two hours following oral challenge with 100 gm. of glucose.

Mean plasma glucose values and rates of suspect glucose intolerance (based on several cutpoints) were sizeably higher in the afternoon than in the morning. In addition, plasma glucose values increased with time elapsed since the last meal, up to 10 hours postprandially. Thereafter, both one- and two-hour plasma glucose values tended to exhibit a decline. Analysis of covariance confirmed that fluctuations in glucose tolerance were related to time of day and time since last meal, but the effects of each parameter were exerted independently. *DIABETES* 25:936-43, October, 1976.

At present, mass screening procedures are being widely employed for the early detection of asymptomatic individuals with predisposition to certain diseases, e.g., clinical diabetes mellitus and premature coronary heart disease. Large-scale surveys often require that populations be screened throughout the day, with little or no possibility of standardizing either time of day or time since last meal. This study

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Accepted for publication May 10, 1976.

was undertaken to determine the relationship of these two time-related parameters to glucose tolerance.

MATERIALS AND METHODS

Population

The 10,559 men and women aged 30-64 reported on in this paper were participants from 1965 to 1971 in a Chicago Health Department multiphasic screening project to detect subclinical chronic diseases and risk factors for these diseases. Among the 13,469 persons surveyed in this project, the 10,559 include all individuals with complete data including time of day and time since last meal when the measurements were taken.¹ The effort was based in two Chicago Housing Authority public housing projects for low-income persons, Dearborn and Lathrop homes, the former on Chicago's near south side with a predominantly black population, and the latter on the near northwest side, with a largely white occupancy. In its initial phase, the screening project intensively encouraged participation by all persons aged 30-64 residing in these two public housing facilities. Subsequently its services were extended to all individuals of this age in the general community of the projects. Persons were excluded from this study who were diagnosed diabetics currently on prescribed antidiabetic medication.

Screening Tests and Biochemical Methods

Persons were scheduled for screening by appointment on a weekday (between 8:30 a.m. and 2:00 p.m.) at times of the morning or afternoon most convenient for them. No instructions were given with regard to dietary preparation.

The battery of standardized screening tests, administered by specially trained teams of nurses and technicians, included an interview to collect demographic data and a brief medical history and the measurement of height and weight. To test glucose tolerance, subjects were given a 100-gm. oral glucose load and venous blood samples were collected in fluoridated tubes one and two hours thereafter.

Plasma was separated within two hours, and analysis was done by the AutoAnalyzer method adapted from Hoffman.² All chemical analyses were performed in the special research laboratory of the Chicago Health Department and Chicago Health Research Foundation, under the direction of Morton B. Epstein, Ph.D., and Howard Adler, Ph.D., at the Chicago Civic Center.

Statistical Methods

All data collected on standardized forms were transferred to computer tapes, tested, and edited for errors prior to computer analyses.

Since the possibility existed that the group of people screened at different times of day might differ significantly in composition in a manner biasing the relationship of time of day and time since last meal to the clinical variables, distributions by age-sex-race and relative weight were used to examine this matter. The principal statistical methods for assessing the relation between time and the clinical variables were

analysis of variance and chi-square.³ An analysis of covariance was used to determine whether the relationships of time of day and time since last meal to postload plasma glucose were independent of each other.

RESULTS

Evaluation of Possible Bias

Data designed to determine whether the composition of the groups of people screened at various times of day and various times since last meal differed markedly from each other in respects, possibly introducing bias into the analyses, are presented in tables 1 and 2. As shown in table 1, the several groups stratified by time of day of screening and time since last meal were not grossly different in their age-sex-race composition. Correspondingly, they were not markedly different in mean age and relative weight (table 2).

Glucose Tolerance by Time of Day and Time Since Last Meal

After the 100-gm. oral glucose load, both one-hour and two-hour mean plasma glucose levels were significantly higher in the afternoon than in the corresponding morning values (table 3 and figure 1). The one-hour mean plasma glucose levels increased with time since last meal in both the morning and afternoon groups, up to 10 hours postprandially; the values for the ≥ 600 -minute groups were lower than the

TABLE 1

Age-sex-race composition of those screened stratified by time of day (morning and afternoon) and time since last meal of ingestion of 100-gm. oral glucose load, Chicago Health Department Community Screening Programs, 1965-1971

Glucose ingestion— Time of day (a.m. and p.m.) and time since last meal—minutes	No. of people	Age-sex-race composition—per cent of row total								All
		White male 30-44	White female 30-44	Black male 30-44	Black female 30-44	White male 45-64	White female 45-64	Black male 45-64	Black female 45-64	
A.M.										
<120	573	7.0	15.4	5.6	20.0	6.1	26.3	6.5	13.1	100.0
120-179	1,303	6.8	17.8	4.9	15.7	10.1	21.9	5.8	17.0	100.0
180-239	1,228	5.1	20.0	3.3	15.4	8.4	27.9	4.8	15.1	100.0
240-299	461	3.7	16.9	5.9	18.0	7.8	22.1	6.7	18.9	100.0
300-419	171	5.8	18.7	7.0	18.7	7.6	15.8	8.2	18.2	100.0
420-599	213	7.5	14.6	9.9	24.4	7.0	11.7	8.0	16.9	100.0
≥ 600	1,673	5.3	19.2	5.4	24.4	6.9	16.4	5.6	16.8	100.0
Total morning	5,622	5.7	18.3	5.3	19.3	8.2	20.8	5.8	16.6	100.0
P.M.										
<120	535	7.8	14.3	4.3	23.9	8.4	24.1	5.2	12.0	100.0
120-179	1,223	7.3	17.6	3.6	19.0	9.2	24.0	4.3	15.0	100.0
180-239	1,112	4.9	15.9	3.7	19.6	7.6	23.8	5.6	18.9	100.0
240-299	851	5.6	16.6	4.6	19.5	8.1	22.8	4.5	18.3	100.0
300-419	818	4.6	15.6	4.0	19.9	7.1	24.7	4.2	19.9	100.0
420-599	163	3.7	14.1	5.5	20.9	6.7	24.5	9.2	15.4	100.0
≥ 600	235	7.2	11.9	8.1	24.7	9.4	20.4	3.0	15.3	100.0
Total afternoon	4,937	5.9	16.0	4.2	20.2	7.9	23.6	4.7	17.5	100.0
Total population	10,559	5.8	17.2	4.8	19.7	8.1	22.1	5.3	17.0	100.0

TABLE 2

Mean age and relative weight of those screened stratified by time of day (morning and afternoon) and time since last meal of ingestion of 100-gm. oral glucose load, Chicago Health Department Community Screening Programs 1965-1971

Glucose ingestion— time of day (a.m. or p.m.) and time since last meal (min.)	No. of people	Mean age —years	Mean relative weight*
A.M.			
<120	573	45.4	1.139
120-179	1,303	46.4	1.154
180-239	1,228	46.8	1.153
240-299	461	46.2	1.177
300-419	171	45.0	1.178
420-599	213	43.7	1.181
≥600	1,673	44.4	1.168
Total morning	5,622	45.6	1.160
P.M.			
<120	535	45.1	1.160
120-179	1,223	46.0	1.152
180-239	1,112	46.5	1.157
240-299	851	45.9	1.168
300-419	818	46.6	1.182
420-599	163	46.7	1.200
≥600	235	44.3	1.181
Total afternoon	4,937	46.0	1.165
Total population	10,559	45.8	1.162

*Relative weight is the ratio of observed weight to desirable weight for sex and height, as obtained from actuarial tables.⁴

preceding 420-599-minute groups, but still elevated in comparison to levels secured closer to the time of the preceding meal.

The two-hour mean plasma glucose levels exhibited a similar increase with time since last meal (table 3 and figure 1). For the morning strata, the highest meal value was again recorded in the 420-599-minute group. For the afternoon strata, the peak value was in the 300-419-minute group.

All two-hour mean plasma glucose values were lower than those of the corresponding one-hour levels (table 3 and figure 1). Analysis of covariance confirmed that postload plasma glucose values were related to both the time of day and the time since last meal but that these two variables exerted their influence on plasma glucose independently.

Results consistent with the foregoing were obtained when the data were analyzed to determine relationship of rate of suspect glucose intolerance to time of day (a.m. vs. p.m.) and time since last meal (table 4). For this purpose, use was made of fixed cut points (>200 and >140 mg./dl. for the one-hour and two-hour postload plasma glucose, respectively), and quantile cut points (upper 5 per cent, 10 per cent, 20 per cent of both the one-hour and two-hour postload distribu-

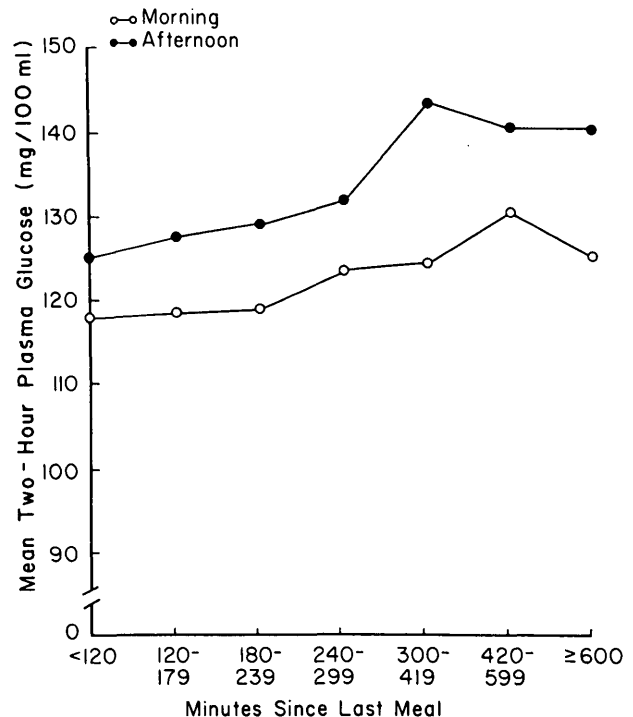
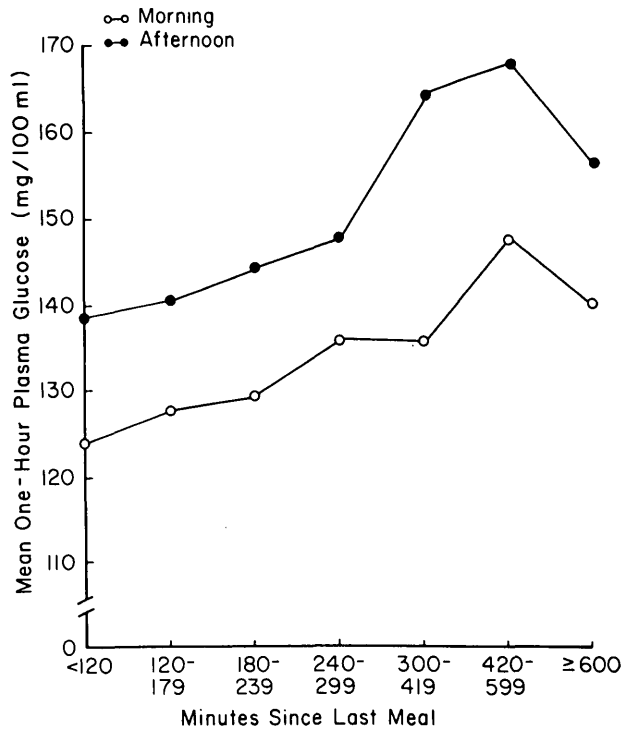


FIG. 1. Relationship of time of day and time since last meal to one-hour (upper graph) and two-hour (lower graph) post-load (100 gm.) plasma glucose.

tions); the levels in mg./dl. for the quantile cut points are given in table 4. As judged by conventional criteria measuring glucose intolerance,⁵⁻⁷ the preva-

TABLE 3

Relationship of mean postload plasma glucose to time of day and time since last meal of ingestion of 100-gm. oral glucose load, Chicago Health Department Community Surveys, 1965-1971

Glucose ingestion— time of day and time since last meal —minutes		Number of persons	1-Hour plasma glucose —mean and standard deviation	2-Hour plasma glucose —mean and standard deviation
Morning				
	< 60	60	118.9 ± 33.2	110.4 ± 23.9
	60-119	513	124.6 ± 53.9	118.8 ± 52.0
	120-179	1,303	127.3 ± 58.6	118.5 ± 57.0
	180-239	1,228	129.4 ± 52.5	119.2 ± 47.9
	240-299	461	135.7 ± 56.1	123.9 ± 51.4
	300-419	171	135.6 ± 61.9	124.7 ± 61.1
	420-599	213	147.5 ± 73.5	130.2 ± 77.9
	≥600	1,673	140.1 ± 63.9	125.1 ± 63.4
	Total morning	5,622	132.9 ± 59.2	121.6 ± 57.2
Afternoon				
	< 60	44	126.5 ± 31.8	109.7 ± 22.7
	60-119	491	138.8 ± 56.1	125.7 ± 52.5
	120-179	1,223	141.6 ± 58.8	127.5 ± 55.4
	180-239	1,112	144.1 ± 63.2	129.2 ± 57.0
	240-299	851	147.6 ± 56.3	132.0 ± 52.2
	300-419	818	164.1 ± 61.8	143.4 ± 60.2
	420-599	163	167.7 ± 58.9	140.6 ± 59.3
	≥600	235	156.3 ± 67.9	140.2 ± 71.0
	Total afternoon	4,937	148.1 ± 60.6	132.0 ± 56.9
All				
	< 60	104	122.1 ± 32.6	110.1 ± 23.3
	60-119	1,004	131.5 ± 55.4	122.2 ± 52.3
	120-179	2,526	134.2 ± 59.1	122.9 ± 56.4
	180-239	2,340	136.4 ± 58.3	123.9 ± 52.6
	240-299	1,312	143.4 ± 56.5	129.2 ± 52.1
	300-419	989	159.2 ± 62.7	140.2 ± 60.7
	420-599	376	156.2 ± 68.2	134.7 ± 70.6
	≥600	1,908	142.1 ± 64.6	127.0 ± 64.6
	Total population	10,559	140.0 ± 60.3	126.5 ± 57.3

lence rate was sizably and significantly higher in the afternoon than in the morning for both the one-hour and two-hour values. For seven of eight morning analyses and all eight afternoon analyses, the trend toward higher rates with increasing time since last meal was statistically significant ($p \leq 0.05$); in 11 of these 16 analyses, p was ≤ 0.001 . Further in accord with the findings for the mean postload plasma glucose values, prevalence rates for suspect glucose intolerance were highest at 300-419 or 420-599 minutes after last meal in five of eight morning analyses and all eight afternoon analyses (six of these latter eight being for the interval 300-419 minutes); for three of the eight morning analyses, this rate was highest for the interval ≥ 600 minutes since the last meal (table 4).

DISCUSSION

Oral ingestion of simple sugars followed by the monitoring of subsequent blood levels has been em-

ployed as a diagnostic tool in the elucidation of perturbations in carbohydrate metabolism for over half a century.⁸ The test has been under much critical scrutiny over the years, as several variables have been determined to be sources of bias that could undermine the diagnostic value of the technique,⁹ and corrective measures have been suggested.⁶ The present studies were designed to measure the effects of time of day and time since last meal on blood sugar response to standard oral glucose challenge in an epidemiologic context.

With a test population of 10,559 subjects, we have found that (a) a significantly greater proportion of "abnormal" blood sugar elevations occur during screening in the afternoon than in the morning; and (b) the proportion of "abnormal" responses at either time of day is lowest when oral glucose is given shortly after a meal and highest when the challenge occurs 5-10 hours following prior alimentation.

TABLE 4
Relationship of suspect glucose intolerance (based on several criteria)⁶⁻⁷ to time of day and time since last meal of ingestion of 100 gm. oral glucose, Chicago Health Department Community Surveys, 1965-1971

Glucose ingestion— time of day (a.m. and p.m.) and time since last meal—minutes	No. of people	1-Hour plasma glucose			2-Hour plasma glucose			Upper 20% cut point (>143 mg./dl.)
		>200 mg./dl. cut point	Upper 5% cut point (>240 mg./dl.)	Upper 10% cut point (>205 mg./dl.)	Upper 5% cut point (>202 mg./dl.)	Upper 10% cut point (>169 mg./dl.)		
A.M.								
< 60	60	0§	0	0	0	0	0	†
60-119	513	31	17	28	55	55	33	67
120-179	1,303	84	50	78	160	160	87	179
180-239	1,228	99	39	80	179	179	83	195
240-299	461	46	18	40	84	84	38	83
300-419	171	19	8	18	29	29	17	30
420-599	213	24	11	22	46	46	24	38
≥600	1,673	186	97	169	331	331	152	305
Total morning	5,622	489	240	435	889	889	435	903
P.M.								
< 60	44	2	0	2	4	4	0	†
60-119	491	50	21	43	91	91	43	88
120-179	1,223	131	55	120	254	254	121	235
180-239	1,112	133	61	123	248	248	120	253
240-299	851	126	47	117	223	223	52	229
300-419	818	175	83	162	307	307	83	299
420-599	163	35	10	32	62	62	28	49
≥600	235	44	19	38	68	68	36	64
Total afternoon	4,937	696	296	637	1,257	1,257	637	1,220
All								
< 60	104	2	0	2	9	9	0	9
60-119	1,004	81	38	71	146	146	76	155
120-179	2,526	215	105	198	414	414	208	414
180-239	2,340	232	100	203	427	427	203	448
240-299	1,312	172	65	157	307	307	155	312
300-419	989	194	91	180	336	336	189	329
420-599	376	59	21	54	108	108	52	87
≥600	1,908	230	116	207	399	399	188	369
Total population	10,559	1,185	536	1,072	2,146	2,146	1,074	2,123

The symbols at the head of the column for the A.M. and P.M. values indicate whether the differences in rate of suspect glucose intolerance (based on the specified criterion) are statistically significant. The chi-square statistic was used for this test; since in six of 16 instances no persons were suspected of glucose intolerance in the small groups of persons tested at <60 min. after last meal, these groups (60 and 44 persons, respectively) were combined with the next group (515 and 491 persons, respectively) for the chi-square tests.

*p ≤ 0.05

†p ≤ 0.01

‡p ≤ 0.001

§No. of people.

¶Rate per 100.

With regard to the first observation, some evidence for a decrease of glucose tolerance in the afternoon and evening has been noted in smaller series during previous assessments of circadian trends in carbohydrate metabolism.¹⁰⁻¹⁸ The phenomenon has been seen with both oral^{10,11,13-18} and intravenous^{12,16} administration of the glucose load, so that factors involving intestinal absorption or secretagogues do not seem to play a key role. Dietary changes also do not appear to be critical, since subjects fed identical meals at different times of the day exhibited decreased glucose tolerance between morning and afternoon tests.^{12,14} Finally, several studies have found higher levels of plasma immunoreactive insulin in the morning than in the afternoon,^{14,16,19} and such cyclicity has even been noted in fasting subjects.¹⁹ Thus, these fluctuations must be construed to be a product of an endogenous pattern, responsive to, but independent of, dietary input. Whether the cyclicity is mediated by diurnal changes in the interactions between insulin and insulin antagonists in the periphery or by alterations in beta cell responsiveness to glycemic stimuli^{17,20} or both¹⁹ cannot be resolved from existing data. Indeed, as yet the effects of wakefulness per se have not been examined critically.¹⁹ For the moment, however, the unequivocal a.m. versus p.m. differences highlight the necessity to consider time of day in any epidemiologic monitoring of carbohydrate function.

Our second observation—that the interval between prior eating and glucose challenge may affect the magnitude of blood sugar responses—has been noted by others^{15,21-27} but not previously recognized as fully independent of the influence of time of day. This finding is not unexpected when viewed in the light of certain theoretical considerations.²⁸ Immediately following alimentation, insulin release is triggered, anabolism is initiated, and circulating contra-insulin factors such as glucagon²⁹ and growth hormone³⁰ are reduced. Administration of a second glucose load at this time should effect facilitated glucose disposition, since islet responsiveness to additional secretagogues should be enhanced by nutrient priming³¹ and tissue sensitivity to insulin should be optimal.³² Earlier observations are consistent with these expectations.²¹⁻²⁴ Thus, Bang,²¹ Hamman and Hirschman,²² and subsequently Staub²³ and Traugott²⁴ noted that blood sugar rises less when a second dose of oral glucose is given within four hours of the first (the "Staub-Traugott effect"). The same phenomenon has been noted following repetitive administrations of in-

travenous glucose, and the enhanced glucose disposition under these circumstances does not necessitate commensurate increases in the rate of insulin secretion.²⁶ Indeed, the ability to sustain tissue "insulinization" independent of exogenous renewal has been demonstrated in an in-vitro model with lipogenesis as the metabolic parameter.³³ On the other hand, coincidentally with the late disposition of exogenous nutrients, counterregulatory hormones would be called into play.²⁸ Their capacity to offset the effectiveness of insulin action has been fully demonstrated for growth hormone^{30,34} and may be equally applicable to hormones such as glucagon, which also rise following disposition of dietary carbohydrates.²⁹ Moreover, tissue metabolism would be geared to lipid products (of dietary as well as endogenous origin) so that the acute disposition of newly introduced glucose might be compromised.³⁵ The temporal characteristics of the sequence would be conditioned by the precise mixture of nutrients in the antecedent meal.³⁶⁻³⁸ Within the above formulation, one might predict that tolerance to a given glucose challenge should be (a) optimal shortly following a meal, (b) compromised during the counterregulation to previous alimentation (i.e., 5-10 hours, depending on the exogenous substrate mixture), and (c) restored to basal (consistent with the time of day) when disposition of all exogenous nutrients has been completed. Our present finding that glucose tolerance is not fully restored until more than seven hours have elapsed is consistent with the above speculative sequence. Clearly, however, definitive interpretation will have to await more careful correlations with concurrent plasma levels of insulin and contra-insulin hormones, as well as with the exact composition of the antecedent meal.

Regardless of the theoretical implications, these observations on relationship of glucose tolerance to time of day and time since last meal need to be evaluated in terms of their relevance to public health practice. As part of the current emphasis on early detection of symptomatic individuals at risk for the development of various diseases, mass screening is increasingly regarded as an efficacious technique. By its very nature, mass screening is usually incompatible with standardization of time of day or time since last meal. To reach large target populations efficiently in the community or the work place, screening often must be done over a wide range of hours and without alteration of people's daily routine. In view of the present findings, the question therefore arises: would it be useful to apply

varying cut points for suspect hyperglycemia at primary screening based on time of day and/or time since last meal? If a single cut point is used, based on experience with a fasted population given an oral load and tested in the morning, there is the possibility of reporting an inordinate number of false positives when screening in the afternoon.^{14,16} This could result in a more than reasonable share of expenditures for complete glucose tolerance testing for these putative "hyperglycemics," as well as a more than reasonable burden of concern for health status. If a single cut point is set high enough to avoid this problem, persons truly at risk may not be detected during morning screening. On the other hand, challenge in the afternoon and/or five to seven hours after meals in which the usual criteria for "normal" and "abnormal" responses are retained⁵⁻⁷ may be useful for unmasking the vulnerable—analagous, for example, to the cortisone-glucose tolerance test.³⁹ Without long-term follow-up studies to determine the prognostic significance of various responses, this issue does not appear to be readily resolvable.

ACKNOWLEDGMENTS

It is a pleasure to acknowledge the cooperation and support of Eric Oldberg, M.D., President, Chicago Board of Health, and Chairman, Board of Directors, Chicago Health Research Foundation. It is also a pleasure to pay tribute to the entire staff of the Heart Disease Control Program, Division of Adult Health and Aging, Chicago Health Department, and of the Chicago Health Research Foundation, aiding in this research, especially Howard Adler, Ph.D., Morton B. Epstein, Ph.D., and Ray Restivo; also Juanita Chestang, Jean Civinelli, Roberta Crawford, Nancy Dalton, Sammie Ellis, Gail Pacelli, Edna Pardo, Frances Petersen, Peggy Powell, R. Raphaelson, Margie Shores, Eve Smolin, Tom Tokich, and Ika Tomaschewsky. It is also a pleasure to express appreciation to the Chicago Housing Authority for its cooperation in this effort.

This research was supported by the Chicago Heart Association; the National Heart and Lung Institute, National Institutes of Health (Research grant HL15174); and the National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health (Research Grant AM-10699 and Training Grant AM-05071).

The work was done while Alan Dyer was an Established Investigator of the American Heart Association.

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