International Medical Journal

Volume 16, Number 2 June, 2009

The Use of HbA_{1C} in the Diagnosis of Type 2 Diabetes Mellitus among High Risk Group in Hospital Universiti Sains Malaysia

Hasni Ibrahim, Shaiful Bahari Ismail, Shamsunarnie Mohamed Zukri, Adibah Hanim Ismail, Wan Mohamad Wan Bebakar

INTERNAL MEDICINE

The Use of HbA_{1C} in the Diagnosis of Type 2 Diabetes Mellitus among High Risk Group in Hospital Universiti Sains Malaysia

Hasni Ibrahim[1], Shaiful Bahari Ismail[1], Shamsunarnie Mohamed Zukri[2], Adibah Hanim Ismail[1], Wan Mohamad Wan Bebakar[3]

ABSTRACT

Introduction: **To improve the detection rate of type 2 diabetes, alternative approach to screening have been proposed, such as lower threshold for FPG or the use of HbA_{1c}. Compared with OGTT, HbA_{1c} measurement is quicker, more convenient, and avoids the need for fasting.**

Objectives: **This study was conducted to evaluate the use of HbA_{1c} as a diagnostic test for diabetes in high risk patient attending Outpatient Clinic at Hospital Universiti Sains Malaysia (HUSM) and to see whether HbA_{1c} is a highly specific test and a convenient alternative to fasting plasma glucose (FPG) or 2-hour postprandial (2-hPP) for diabetes screening.**

Method: **Measurement of FPG, 2-hPP and HbA_{1c} level were performed in 200 subjects, aged 35 years and above with capillary blood glucose ≥ 5.6 mmol/L. The subjects also have at least one cardiovascular risk factor.**

Results: **The mean age and body mass index for study sample were 52.4±9.6 and 26.7±5.0 respectively. The mean of FPG level was 5.7±2.3 mmol/dL, mean of 2-hPP level was 10.0±5.3 mmol/dL and HbA_{1c} level was 6.1±1.5%. Of 200 patients, 40.0% (n = 80) was diagnosed as normal glucose tolerance, 25.5% (n = 51) had impaired fasting glucose and/or impaired glucose tolerance and 34.5% (n = 69) had type 2 diabetes mellitus. The HbA_{1c} of 7.0% gave an optimal sensitivity of 82% and specificity of 91% to predict a FPG ≥ 7.0 mmol/dL. Whereas, HbA_{1c} of 6.4% with sensitivity and specificity of 68% and 87% respectively was an optimal value to predict 2-hPP ≥ 11.1mmol/dL. All together, an HbA_{1c} of 6.4% gave an optimal sensitivity of 68% and specificity of 89% to predict both FPG ≥ 7.0 mmol/dL and/or 2-hPP ≥ 11.1mmol/dL.**

Conclusion: **HbA_{1c} has good sensitivity and specificity to diagnose abnormal glucose tolerance and types 2 diabetes mellitus.**

KEY WORDS

hemoglobin A_{1C} (HbA_{1c}), fasting plasma glucose (FPG), 2-hour postprandial (2-hPP)

INTRODUCTION

For many years, the diagnosis of Diabetes Mellitus has depended primarily on results of OGTT. The OGTT is the gold standard for diagnosing type 2 diabetes mellitus. It has limited use for mass screening, due to need for fasting, the time consuming nature of the test, and poor reproducibility of the results.

To improve the detection rate of type 2 diabetes, alternative approach to screening have been proposed, such as lower threshold for FPG or the use of HbA_{1c}. Compared with OGTT, HbA_{1c} measurement is quicker, more convenient, and avoids the need for fasting[1]. HbA_{1c} was noted to be highly specific (91%); an elevated HbA_{1c} usually indicate diabetes or IGT. A normal HbA_{1c} did not however

Received on August 22, 2008 and accepted on October 30, 2008

1) Department of Family Medicine, School of Medical Sciences, Universiti Sains Malaysia
16150 Kubang kerian, Kelantan Malaysia
2) Department of Science, Technology and Quantitative, Universiti Teknologi
MARA Pulau Pinang 13500 Permatang Pauh, Pulau Pinang Malaysia
3) Department of Medicine, School of Medical Sciences, Universiti Sains Malaysia
16150 Kubang kerian, Kelantan Malaysia
Correspondence to: Shaiful Bahari Ismail
(e-mail: shaifulbahari67@yahoo.com)

Table 1. Modified criteria for interpretation of Oral Glucose Tolerance Tests (OGTT)

	Normal	IFG/IGT	Diabetes
Fasting plasma glucose (FPG)	< 5.6 mmol/L	5.6-6.9 mmol/L	≥ 7.0 mmol/L
2 hour postprandial (2-hPP)	< 7.8 mmol/L	7.8-11.0 mmol/L	≥ 11.1 mmol/L

Abbreviations: IFG, impaired fasting glucose; IGT, impaired glucose tolerance

exclude the diagnosis of diabetes or IGT[2].

In one of the studies to evaluate the use of HbA_{1c} as a screening instrument for undiagnosed diabetes in US population, it was found that with a cut-off level for HbA_{1c} of 6.1% (2 SD above normal) the sensitivity was 63.2% and the specificity was 97.4%. Therefore HbA_{1c} is a highly specific and convenient method to use in screening for undiagnosed diabetes, and that a value of 2 SD above the upper normal mean could identify a large proportion of individuals with undiagnosed diabetes who are at risk of developing late diabetic complications[3].

This study was conducted to evaluate the use of HbA_{1c} as a diagnostic test for diabetes in high risk patient attending Outpatient Clinic at Hospital Universiti Sains Malaysia (HUSM) and to see whether HbA_{1c} is a highly specific test and a convenient alternative to fasting plasma glucose (FPG) or 2-hour postprandial (2-hPP) for diabetes screening.

MATERIALS AND METHODS

Study design and study sample

A cross-sectional study was conducted to evaluate the optimal cutoffs of HbA_{1c} as a diagnostic test for diabetes in high risk patienst attending Outpatient Clinic, Hospital Universiti Sains Malaysia. The study period was during January 2005 to August 2005. The study samples were patients with high risk of developing diabetes with positive screen using dextrose stick glucose.

Inclusion and exclusion criteria

The participants in this study must fulfill all the criteria to be included in this study which were age ≥ 35 years; have one or more cardiovascular risk; and positive screen using dextrose stick glucose ≥ 5.6 mmol/l. The person with previous diagnosis of diabetes; pregnancy; and history of haemolytic anaemia, haemoglobinopathies and renal failure was excluded.

Data collections

Patients attending Outpatient Clinic, HUSM during study period who fulfilled the inclusion and exclusion criteria and consented to participate in study were included in this study. Patient will complete questionnaires on demographic data and risk factors for developing type 2 diabetes mellitus (DM). Appointment was given to patient for OGTT. Patient was asked to fast from 10 pm and return to the clinic at 8 am the next morning for fasting plasma glucose. At the same time blood was drawn for HbA_{1c}. Accordingly, 75 g oral glucose in 300 mls of water was given to the patient and plasma glucose at 120 minutes was obtained. All results for FPG and 2-hPP were classified as stated in Table 1.

Principle of procedure for HbA_{1c}

The D10 Hemoglobin A_{1c} Program utilizes principles of ion exchange High Performance Liquid Chromatography (HPLC). The samples are automatically diluted on the D10, injected into the analytical flow path, and applied to analytical cartridge. The D10 delivers a programmed buffer gradient of increasing ionic strength to the cartridge, where the hemoglobins are separated based on their ionic interaction with the cartridge. The separated hemoglobins then pass through the flow cell of the filter photometer, where changes in the absorbances at 415 nm are measured.

Sample size

Sample size was calculated on a 95% confidence interval, sensitivity of 85%[2] and with 8% precision. Primarily, the single proportion sample size formula was applied to calculate the sample size for diabetic patient diagnosed by gold standard. The obtained sample size then divided with the prevalence of diabetes in high risk group (38%, from pilot study). The total sample size for this study was estimated to be about 200 patients.

Statistical analyses

Descriptive statistics were estimated to describe the initial demographic characteristics such as; age, Body Mass Index (BMI), sex and race; and laboratories characteristics which were fasting plasma glucose (FPG), 2 hour postprandial (2-hPP) and Hemoglobin A_{1c} (HbA_{1c}). Mean ± Standard Deviation (SD), frequency and percentage were used to describe the data where appropriate. One-Way ANOVA and Pearson Chi-Square test were performed. The receiver operating characteristic (ROC) was used to find the optimal HbA_{1c} cutoffs, to evaluate the presence or absence of type 2 diabetes and normal or abnormal plasma glucose as defined by the FPG, 2-hPP and both (FPG and 2-hPP). This ROC describes the diagnostic properties in terms of sensitivity and specificity of every interest HbA_{1c} cutoffs. The p-values < 0.05 was considered statistically significant. All the statistical analyses were performed using SPSS software for windows (version 11.5.0; SPSS Inc., Chicago, IL)

RESULTS

A total of 200 patients with at least two risk factors for

Table 2. Initial characteristics of total 200 patients among three groups

Parameter	Normal[a] (n = 80) Mean ± SD or n (%)	IFG and/or IGT (n = 51) Mean ± SD or n (%)	DM (n = 69) Mean ± SD or n (%)
FPG, mmol/dL	4.5±0.5	5.0±0.7	7.6±3.0
2-hPP, mmol/dL	5.8±1.2	8.6±1.3	15.8±4.7
HbA_{1c}, %	5.2±0.6	5.8±0.7	7.3±1.8
Age, y	50.6±9.8	55.0±10.0	52.5±8.7
Body Mass Index	25.6±4.1	27.6±5.2	27.4±5.6
Sex			
Male	42 (46.7)	22 (24.4)	26 (28.9)
Female	38 (34.5)	29 (26.4)	43 (39.1)
Race			
Malay	75 (42.1)	42 (23.6)	61 (34.3)
Non-Malay	5 (22.7)	9 (40.9)	8 (36.4)

Abbreviations: FPG, fasting plasma glucose; 2-hPP, 2 hour postprandial; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; DM, type 2 diabetes mellitus

[a] Normal plasma glucose

Table 3. HbA_{1c} cutoff for different level of glucose plasma diagnosed using FPG; 2-hPP; and both

Standard	HbA_{1c},%		
	Normal	IFT/IGT	DM
HbA_{1c},% with FPG as standard	< 6.1	6.1 - 6.9[a]	≥ 7.0
HbA_{1c},% with 2-hPP as standard	< 5.8	5.8 - 6.3[b]	≥ 6.4
HbA_{1c},% with FPG and/or 2-hPP as standard	< 5.8	5.8 - 6.3[c]	≥ 6.4

Abbreviations: FPG, fasting plasma glucose; 2-hPP, 2 hours postprandial; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; DM, type 2 diabetes mellitus

[a]IFG (FPG < 5.6 mmol/L); [b]IGT (2-hPP < 7.8 mmol/L); [c]IFG and/or IGT (FPG ≥ 7.0 mmol/L and/or 2-hPP ≥ 11.1 mmol/L)

diabetes underwent a fasting plasma glucose (FPG), 2 hour postprandial (2-hPP) and HbA_{1c}.The overall mean ± SD age of patients was 52.4±9.6 year. The mean ± SD of FPG, 2-hPP and HbA_{1c} was 5.7±2.3 mmol/dL, 10.0±5.3 mmol/dL and 6.1±1.5% respectively. Out of 200 patients, 45% were male and majority of patients were Malay. Of 200 patients, 35.5% (n = 71) had an abnormal FPG result (44 IFG; 27 DM). In addition, of 200 patients, 56.5% had abnormal 2-hPP result (48 IGT; 65 DM). The incidence of DM was 13.5% based on FPG level ≥ 7.0 mmol/dL; 32.5% based on 2-hPP level ≥ 11.1 mmol/dL and 34.5% based on both ≥ 7.0 mmol/dL and/or 2-hPP level ≥ 11.1 mmol/dL.

The characteristics of patients with normal glucose tolerance, IFG/IGT and type 2 diabetes groups were presented in Table 2. The mean value of HbA_{1c} among patients with normal glucose tolerance, IFG/IGT and type 2 diabetes was 5.2%, 5.8% and 7.3% (Table 2). The mean ± SD HbA_{1c} among 200 patients, when considering FPG as standard were 5.4±0.7% in normal glucose tolerance group; 6.5±1.0% in IFG groups; and 8.6±1.9% in type 2 diabetes group. Furthermore, by using 2-hPP measurement alone, the mean ± SD HbA_{1c} for normal; an IGT and type 2 diabetes group was 5.2±0.6%; 6.0±0.8%; and 7.3±1.8% respectively.

The HbA_{1c} optimal cutoffs for different level of glucose plasma diagnosed using FPG; 2-hPP; and both. The HbA_{1c} cutoffs were the same between using 2-hPP and both (FPG and/or 2-hPP), except with the different sensitivity and specificity values (Table 3 and 4).

The HbA_{1c} value ≥ 6.1% with the sensitivity and specificity estimated at 80% and 89% respectively was the optimal cutoff to diagnose abnormal FPG level (≥ 5.6 mmol/dL). The HbA_{1c} of ≥ 7.0% gave an optimal sensitivity 82% and specificity 91% to predict FPG ≥ 7.0 mmol/dL. The use of HbA_{1c} ≥ 5.8% with the sensitivity 78% and specificity 82% can be a convenient alternatives to diagnosed abnormal 2-hPP level ≥ 7.8 mmol/dL, while cutoff of HbA_{1c} ≥ 6.4% with the sensitivity 68% and specificity 87% was suggested to predict 2-hPP ≥ 11.1 mmol/dL. The use of HbA_{1c} cutoff 5.8% with sensitivity 76% and specificity 84% was suggested for predicting the normal and abnormal FPG and/or 2-hPP. Furthermore, FPG and/or 2-hPP as standard, HbA_{1c} ≥ 6.4% was predicted type 2 diabetes with the sensitivity of 68% and specificity of 89 % (Table 4).

Table 5 showed the initial characteristics of 200 patients with proposed HbA_{1c} cutoff for diagnosed abnormal plasma glucose and type 2 diabetes. Among 129 patients with normal FPG concentrations, HbA_{1c} levels were normal in 69.0%, slightly elevated in 20.9% and high in 10.1%. Among 44 patients with IFG, HbA_{1c} levels were range from 5.8-6.3% in 31.8%. Among 27 patients with DM diagnosed by FPG, 92.6% had high HbA_{1c} values (Table 5).

Table 4. Sensitivity and specificity of HbA_{1c} cutoff with abnormal glucose plasma and diabetes level diagnosed by FPG; 2-hPP; and both

Standard	Abnormal glucose plasma			Type 2 diabetes		
	HbA_{1c}, %	Se (%)	Sp (%)	HbA_{1c}, %	Se (%)	Sp (%)
Fasting Plasma Glucose	6.1	80	89	≥ 7.0	82	91
2 hours postprandial	5.8	78	82	≥ 6.4	68	87
Both	5.8	76	84	≥ 6.4	68	89

Abbreviations: FPG, fasting plasma glucose; 2-hPP, 2 hours postprandial

Table 5. The initial characteristics of 200 patients with proposed HbA_{1c} cutoff for diagnosed abnormal plasma glucose and type 2 diabetes mellitus

Parameter	HbA_{1c} Group, %			*P*-value
	< 5.8	5.8 - 6.3	≥ 6.4	
No. of patients, n (%)	96 (48)	42 (21)	62 (31)	-
FPG, mean ± SD, mmol/dL	4.7 ± 0.8	5.3 ± 0.8	7.7 ± 3.2	< 0.001
2-hPP, mean ± SD, mmol/dL	6.9 ± 2.5	10.0 ± 3.5	15.11 ± 5.7	< 0.001
HbA_{1c}, mean ± SD, %	5.1 ± 0.5	6.0 ± 0.2	7.8 ± 1.5	< 0.001
Age, mean ± SD, y	50.4 ± 9.4	56.7 ± 11.5	52.6 ± 7.8	0.003
BMI, mean ± SD	25.8 ± 4.6	27.4 ± 4.2	27.8 ± 5.8	0.036
Sex, Male/Female, %	47.2/52.8	44.4/55.6	40.4/59.6	0.092
Race, Malay/Non-Malay, %	89.6/10.4	88.9/11.1	87.7/12.3	0.499
By FPG, n (%)				
Normal	89 (69.0)	27 (20.9)	13 (10.1)	
IFG	6 (13.6)	14 (31.8)	24 (54.5)	
DM	1 (3.7)	1 (3.7)	25 (92.6)	
By 2-hPP, n (%)				
Normal	71 (81.6)	13 (14.9)	3 (3.4)	
IGT	20 (41.7)	13 (27.1)	15 (31.3)	
DM	5 (7.7)	16 (24.6)	44 (67.7)	
By both (FPG and/or 2-hPP), n (%)				
Normal	67 (83.8)	10 (12.5)	3 (3.8)	
IFG/IGT	23 (45.1)	16 (31.4)	12 (23.5)	
DM	6 (8.7)	16 (31.4)	47 (23.5)	

Abbreviations: FPG, fasting plasma glucose; 2-hPP, 2 hour postprandial; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; DM, type 2 diabetes mellitus

DISCUSSIONS

Glycosylated haemoglobin is an important monitoring tool but ADA (1998) does not recommend it for screening or diagnostic method at this time because of "the many different methods for the measurement of GHb" and because "nationwide standardization of GHb test had just begun"[4].

However, the National Glycohaemoglobin Standardization Program (NGSP) has obviated these issues by making standardization of GHb methods widely available[5]. The NGSP certifies manufacturers' GHb testing methods as traceable to the Diabetes Control and Complications Trial (DCCT) reference. Therefore, results from NGSP-certified methods are comparable between methods and laboratories, as demonstrated by recent College of American Pathologists survey data, and can be directly related to DCCT-determined risks for the development of microvascular complications[6].

The ADA has recommended that only NGSP-certified methods be used to measure GHb[7], and most of the major GHb assay methods currently in use are certified by the NGSP[8]. Peters and associates (1996) suggested use of a glycosylated haemoglobin A_{1C} (HbA_{1c}) value of 7.0% as the cutoff for detecting "treatment-requiring diabetes". They argued that the clinical approach to a patient with an HbA_{1c} below 7.0% would be the same regardless of OGTT results and that pharmacologic agent are rarely prescribed for such patients[1].

In this study the diagnosis of diabetes was defined on the basis of results from a single OGTT, which is a similar approach to many previous epidemiological studies that studied the prevalence, incidence, and burden of diabetes[9]. This is not in keeping with the current ADA or WHO guidelines, which require either two tests to be abnormal or one test to be positive on two separate occasions. This approach, though not optimal, is representative of the practice situation and has provided meaningful data.

The incidence of type 2 diabetes diagnosed by 2-hPP and both FPG and/or 2-hPP was comparable with type 2 diabetes

diagnosed using proposed HbA_{1c} cutoff (≥ 6.4%) which was 32.5% (by 2-hPP) and 34.5% (by both FPG and/or 2-hPP). We noted that FPG underestimate incidence of type 2 diabetes (13.5%) compared to others which 33.5% in average.

This study data resulted that the HbA_{1c} cutoff (≥ 7.0%) was similar with current cutoff by FPG (≥ 7.0 mmol/dL) to diagnose type 2 diabetes. Interestingly all HbA_{1c} cutoff values such as normal plasma glucose, abnormal plasma glucose; and type 2 diabetes were similar by using either 2-hPP or both FPG and/or 2-hPP as a gold standard. Compare to the study by R.Clark *et al*, the HbA_{1c} to predict FPG levels between 5.5 and 8.0 mmol/L was > 6.1%, whereas this study noted HbA_{1c} cutoff ≥ 6.1% and ≤ 6.9% to predict FPG values between 5.6 and 6.9 mmol/dL.

Our study found the HbA_{1c} cutoff ≥ 6.4% with reasonable sensitivity (68%) and specificity (87%) to predict 2-hPP ≥ 11.1 mmol/dL. Tarekegn et al, suggest cutoff HbA_{1c} of 5.6% with sensitivity (72%) and specificity (77%) to predict 2-hPP ≥ 7.8 mmol/L[10].

Lastly, we found that HbA_{1c} cutoff < 5.8%; 5.8-6.3%; and ≥ 6.4% to diagnosed normal plasma glucose; abnormal plasma glucose; and type 2 diabetes among high risk group people.

CONCLUSION

HbA_{1c} is a convenient alternative to FPG, 2-hPP and both FPG and/or 2-hPP test to diagnose abnormal glucose tolerance levels or types 2 diabetes with good sensitivity and specificity.

ACKNOWLEDGEMENT

The authors would like to acknowledge the Research and Ethical Committee of Universiti Sains Malaysia for their approval and grants for us to conduct the study. We would also like to acknowledge the assistance of the staffs at the Outpatient Clinic, HUSM.

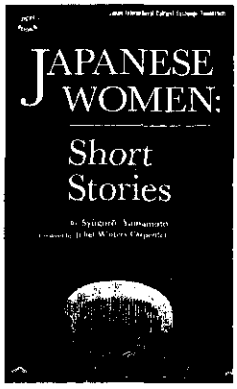
REFERENCES

1) Peters AL, Davidson MB, Schriger DL, *et al.* A clinical approach for the diagnosis of diabetes mellitus: an analysis using glycosylated haemoglobin levels. Meta-analysis research group on the diagnosis of diabetes using glycated haemoglobin levels. JAMA 1996; 276(15): 1246-1252.
2) Randie RL, *et al.* Relationship of glycosylated haemoglobin to oral glucose tolerance: implication for diabetes screening. *Diabetes* 1988; 37: 60-64.
3) Rohlfing CL, *et al.* Use of GHb (HbA_{1c}) in screening for undiagnosed diabetes in the US population. *Diabetes Care* 2000; 23(2): 187-91.
4) American Diabetes Association. Screening for type 2 diabetes (Position Statement). Diabetes Care 1998; 21(Suppl 1): S20-S22.
5) Goldstein DE, Little RR. Bringing order to chaos: standardizing the Haemoglobin A1c assay. Contemp Int Med 1997; 9: 27-32.
6) Little RR, Myers GL, Nathan D, Steffes MW, Gunter EW, Messenger LJ, Parker KM, Robbins DC, Reed RG, Eckfeldt J, Goldstein DE. Implementation of the National Glycohemoglobin Standardization Program (NGSP) in the U.S. Clin Chem Lab Med 1999; 186: 274.
7) American Diabetes Association (ADA). Tests of glycaemia in diabetes (Position Statement). Diabetes 1999; 22(Suppl 1): S77-S79.
8) Goldstein DE. (1998). Isn't it time to retire the oral glucose tolerance test for diabetes screening and diagnosis? (Editorial). Diabetes Care 1998; 21: 1215-1216.
9) Harris MI, Eastman RC, Cowie CC, Flegal KM, Eberhardt MS. Comparison of diabetes diagnostic categories in the U.S. population according to 1997 American Diabetes Association and 1980-85 World Health Organization diagnostic criteria. Diabetes Care 20: 1859-1862.
10) Geberhiwot T, Haddon A, Labib M. HbA_{1c} predicts the likelihood of having impaired glucose tolerance in high-risk patients with normal fasting plasma glucose. *Ann Clin Biochem* 2005; 42.

JICEF BOOKS

The Japan International Cultural Exchange Foundation (JICEF) hopes to improve human culture and promote world peace through international cultural exchange activities.

Titles of Interest :



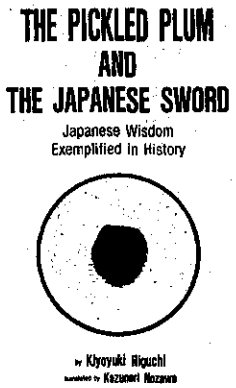
JAPANESE WOMEN : SHORT STORIES

by Shugoro Yamamoto
translated by Juliet Winters Carpenter
240 pages, ¥2,100

The stories help the reader to understand the *bushido* idea of womanhood within a culture that is light years away from the modern era. In this fine translation, eleven tales of constancy, devotion and selfless service mirror aspects of a timeless ideal.

Japanese Women : Short Stories remains one of the best-loved books of Japanese literature today.

Dr. Patricia Morley
Fellow, Simone de Beauvoir Institute
Concordia University, Montreal, Canada



THE PICKLED PLUM AND THE JAPANESE SWORD

by Kiyoyuki Higuchi
translated by Kazunori Nozawa
191 pages, ¥4,200

This book is a gold mine of information about Japanese culture and its origins. Among the valuable nuggets that the reader will find are previously undocumented interrelationships between various cultural phenomena and the place of technology within the earliest culture.

The author, Kiyoyuki Higuchi, was the first Japanese historian to point out that Japanese were not mere imitators, but had the unique ability to adapt and improve cultural and technological imports from other countries.

Prof. Charles E. Adamson, Jr.
Shizuoka Institute of Science and
Technology