History of Contemporary Medicine

Breakthrough Discovery of HbA1c by Professor Samuel Rahbar in 1968

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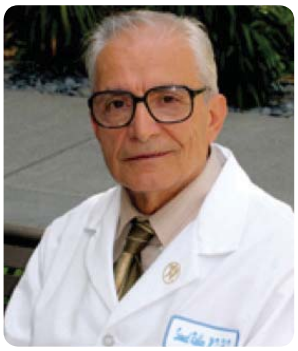


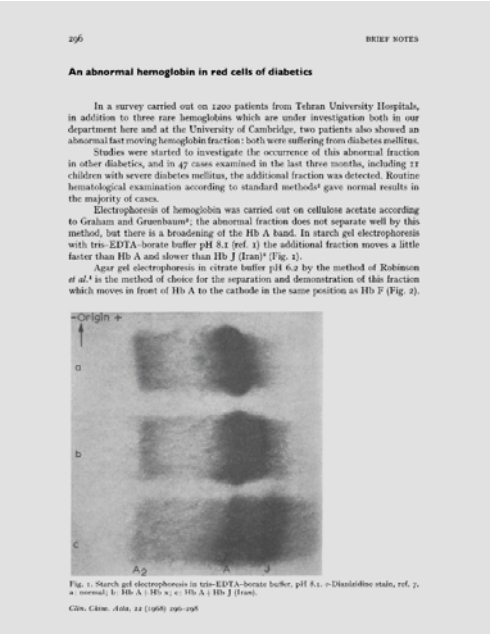
Professor Samuel Rahbar

Professor Samuel Rahbar **(**May 12, 1929 – November 10, 2012) was an outstanding scholar who discovered the presence of an abnormally increased amount of glycated hemoglobin (HbA1c) in the blood of patients with diabetes mellitus. This monumental discovery led to a significant improvement in the diagnosis and management of millions of diabetics all over the world.

From a biochemical point of view, an irreversible non-enzymatic glycation of the beta chain of hemoglobin A results in HbA1c formation which is currently used as a major biological marker and indicator of long-term glycemic control in diabetic patients.[1] The first clinically useful test for HbA1c content was introduced around 1977 to monitor the management of diabetes, although its accuracy was still poor. Then in 1991, the first commercial immunoassay test became available, and HbA1c manual immunoassay analyzer has been in use since 1992.[2] Importantly, the test is now standardized and used world-over and, more recently, for the diagnosis of diabetes.[3]

Samuel Rahbar was born in Hamadan, Iran in 1929. He enrolled in the Tehran University Medical School and graduated in 1953. In due course, Dr. Rahbar practiced medicine in Abadan and Tehran till 1959. Thereafter, he started his postdoctoral immunology fellowship at Tehran University and received his PhD in 1963. He was promoted to Assistant Professor at the Department of Immunology and then became an Associate Professor in 1965.[4]

His influential paper and a genuine breakthrough entitled "Abnormal Hemoglobin in Red Cells of Diabetics" was published in an international journal of clinical chemistry and diagnostic laboratory medicine named *Clinica Chimica Acta* in October 1968. There he wrote: "In a survey carried out on 1200 patients from Tehran University Hospitals, in addition to three rare hemoglobins which are under investigation both in our department here and at the University of Cambridge, two patients also showed an abnormal fast moving hemoglobin fraction: both were suffering from diabetes mellitus." He also added that more studies were initiated to explore the occurrence of this abnormal fraction in other diabetics and HbA1c was detected in 47 cases surveyed within the next three months, including two children with severe diabetes mellitus. In most cases, routine hematological examination according to standard methods yielded normal results (Figure 1).[5] This paper has been cited 344 times.



296 BRIEF NOTES

An abnormal hemoglobin in red cells of diabetics

In a survey carried out on 1200 patients from Tehran University Hospitals, in addition to three rare hemoglobins which are under investigation both in our department here and at the University of Cambridge, two patients also showed an abnormal fast moving hemoglobin fraction: both were suffering from diabetes mellitus.

Studies were started to investigate the occurrence of this abnormal fraction in other diabetics, and in 47 cases examined in the last three months, including 11 children with severe diabetes mellitus, the additional fraction was detected. Routine hematological examination according to standard methods[2] gave normal results in the majority of cases.

Electrophoresis of hemoglobin was carried out on cellulose acetate according to Graham and Gruenbaum[3]; the abnormal fraction does not separate well by this method, but there is a broadening of the Hb A band. In starch gel electrophoresis with tris–EDTA–borate buffer pH 8.1 (ref. 1) the additional fraction moves a little faster than Hb A and slower than Hb J (Iran)[4] (Fig. 1).

Agar gel electrophoresis in citrate buffer pH 6.2 by the method of Robinson *et al.*[5] is the method of choice for the separation and demonstration of this fraction which moves in front of Hb A to the cathode in the same position as Hb F (Fig. 2).

Fig. 1. Starch gel electrophoresis in tris–EDTA–borate buffer, pH 8.1. o-Dianisidine stain, ref. 7. a: normal; b: Hb A + Hb x; c: Hb A + Hb J (Iran).

Clin. Chim. Acta, 22 (1968) 296–298

Figure 1. Professor Rahbar's paper in *Clinica Chimica Acta*, Volume 22, Issue 2, October 1968, Pages 296–298 (Available from: http://dx.doi.org/10.1016/0009-8981(68)90372-0 Accessed 4.9.2013.)

Between 1968 and 1969 , Professor Rahbar was a visiting professor at the Department of Medicine at the "Albert Einstein College of Medicine" in New York and he collaborated with Professor Helen M. Ranney (d. 2010), a pioneering scholar who significantly contributed to the study of sickle cell anemia in children.[6–7]

Upon return to Tehran, Professor Rahbar became full professor in 1970 and was assigned as Director of the Department of Applied Biology at the Medical School of University of Tehran. In addition to HbA1c discovery, Dr. Rahbar examined 220,000 blood samples over a period of 15 years from different hospitals in Tehran and eventually detected 11 new variants of hemoglobin in Iran (Figure 2). For nomenclature of these new hemoglobins, Professor Rahbar used Persian words in his papers such as Iran,

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Avicenna, Persepolis, Kurosh, Arya, Hamadan, Daneshgah-Tehran and Persian Gulf.

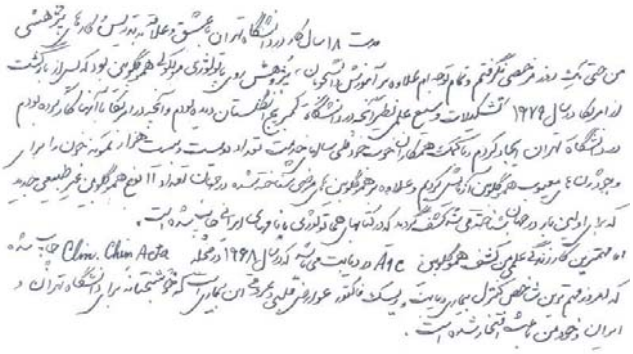

Figure 2. The sample Persian handwriting of Professor Rahbar in part of his letter to Moslem Bahadori MD, Professor of Pathology at Tehran Medical School, 2008. He explained briefly his educational and research efforts in 18 years at the Tehran Medical School including evaluation of 220,000 blood samples for detection of hemglobinopathies, identifying 11 abnormal hemoglobins and his great discovery of increased level of HbA1c in diabetics.

In 1979, he went to United States and joined the Department of Diabetes, Endocrinology and Metabolism at the City of Hope in Duarte, California as researcher and professor of diabetes.[4] According to the American Diabetes Association (ADA), in the last years of his fruitful life, Professor Rahbar continued his researches on DM and his discovery of glycated hemoglobin paved the way for further researches such as advanced glycated end products (AGEs), advanced lipoxidation end products (ALEs) and DNA-AGEs adducts.[8] Professor Rahbar obtained several USA granted patents including "New generation of inhibitors of AGEs" and "Suppression on Receptor for advanced glycation end products (RAGE) expression and RAGE triggered".

In recognition of his discovery of HbA1c, the ADA bestowed a National Scientific Achievement Award on Rahbar in 2012 (Figure 3). The official website of ADA points out that in 1968, Dr. Rahbar reported the elevated level of a rare, fast-moving glycated fraction of hemoglobin, HbA1c, in patients with diabetes. Dr. Rahbar's discovery provided the basis for future work that confirmed HbA1c as a clinically useful marker for long-term glycemic status, and development of the standardized clinical assay now used routinely in clinical practice.[9]

Figure 3. Samuel Rahbar Outstanding Discovery Award.[9]

His published papers

Professor Rahbar authored 107 scientific papers. There are 75 scholarly papers written by Professor Rahbar and his Iranian and non-Iranian colleagues indexed on PubMed, of which 21 papers, from 1967 to 1995, are directly related to Iran. Two of these papers are published in the "Acta Medica Iranica" affiliated with Tehran School of Medicine and others in international journals.[10] Those papers available on PubMed and directly related to Iran include:

- Molecular analyses of beta-thalassemia in Iran. *Hemoglobin*; 1995.
- Splice junction [IVS-II-1 (G-->C)] thalassemia; a new mutation detected in an Iranian patient. 1993.
- Association of hemoglobin H disease with Hb J-Iran (beta 77 His----Asp): impact on subunit assembly. *Blood*; 1987.
- Hemoglobin Avicenna (beta 47 (CD6) Asp replaced by Ala). A new abnormal haemoglobin. *Biochim Biophys Acta*; 1979.
- Hemoglobin Coventry (beta 141 deleted) in Iran. *FEBS Lett*; 1978.
- Hemoglobin Osu-Christiansborg (beta52 (D3) Aspyield Asn) in an Iranian family. *Hemoglobin*; 1978.
- Immunochemical studies in a patient with Waldenstrom's macroglobulinemia. *Acta Medica Iranica*; 1978.
- Hemoglobin Setif [alpha94 (G1) Asp replaced by Tyr] in Iran. A report of 9 cases. *Hemoglobin*; 1977.
- Hemoglobin M Boston in an Iranian family. *Acta Medica Iranica*; 1977.
- Two new hemoglobins: hemoglobin Perspolis [alpha 64 (E13) Asp leads to Tyr] and haemoglobin J-Kurosh [alpha 19 (AB) Ala leads to Asp]. *Biochim Biophys Acta*; 1976.
- A double heterozygous hemoglobin. Hemoglobin OIndonesia and hemoglobin DPunjab in an individual. *Am J Clin Pathol*; 1975.
- Hemoglobin Arya: alpha 2-47 (CD5), aspartic acid yields asparagine. *Biochim Biophys Acta*; 1975.
- Hemoglobin Hamadan: alpha-2A beta-2 56 (D7) glycine yields arginine. *Biochim Biophys Acta*; 1975.
- A case of homozygous hemoglobin Lepore Boston in Iran. *Acta Haematol*; 1975.
- Hemoglobin Lepore Boston in two Iranian families. *Blood*; 1974.
- Hemoglobin Daneshgah-Tehran alpha2 72 (EPI) histidine--arginine betaA2 . *Nat New Biol*; 1973.
- Hemoglobin D Iran: 222 glutamic acid leads to glutamine (B4). *Br J Haematol*; 1973.
- Favism in the Caspian littoral area of Iran. *Trop Geogr Med*; 1971.
- Hemoglobin L Persian Gulf: alpha-57 (E6) glycine leads to arginine. *Acta Haematol*; 1969.
- Hemoglobin H disease in two Iranian families. *Clin Chim Acta*; 1968.
- Abnormal hemoglobins in Iran. Observation of a new variant--hemoglobin J Iran (alpha-2-beta-2 77 His--Asp). *Br Med J*; 1967.

For more than 30 years, Professor Rahbar worked closely with the Persian American community to form the Persian Friends of City of Hope and the Iranian-American Committee for Support of Medical Research. Today, to ensure that Rahbar's work continues in City of Hope laboratories, his family urges the Persian American community to embrace *The Samuel Rahbar Professorship in Diabetes & Drug Discovery*.

Acknowledgment

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References

1. Lahousen T, Roller RE, Lipp RW, Schnedl WJ. Determination of glycated hemoglobins (Hb A1c). *Wien Klin Wochenschr*. 2002; **114(8-9):** 301 – 305.
2. Tattersall RB. The History of Diabetes Mellitus. In: Holt RIG, Cockram CS, Flyvbjerg A, Goldstien BJ, eds. *Textbook of Diabetes*. 4th ed. USA: A John Wiley & Sons, Ltd; 2010:18.
3. Gebel E. The start of something good: the discovery of HbA1c and the American Diabetes Association Samuel Rahbar Outstanding Discovery Award. *Diabetes Care*. 2012; **35:** 2429 – 2431.
4. Garry John BW, Mosca A, Weykamp C, Goodall I. HbA1c Standardization: history, science and politics. *Clin Biochem Rev*. 2007; **28:** 163 – 168.
5. Rahbar S. An abnormal hemoglobin in red cells of diabetics. *Clin Chim Acta*. 1968; **22(2):** 296 – 298.
6. Einstein/Montefiore Department of Medicine. Available from: URL: http://www.einstein.yu.edu/departments/medicine/ medicine.aspx?id=25552 (Accessed 4.9.2013)
7. Rahbar S, Blumenfeld O, Ranney HM. Studies of an unusual hemoglobin in patients with diabetes mellitus. *Biochem Biophys Res Commun*. 1969: **36:** 838 – 843.
8. Available from: URL: http://www.cityofhope.org/about/publications/hope-news/2012-vol-07-num-14-june-4/Pages/samuel-rahbar-will-receive-national-scientific-and-health-care-achievement-award-for-diabetes-work.aspx (Accessed 4.9.2013)
9. Available from: URL: http://www.diabetes.org/about-us/national-achievement-awards-2012/national-science-and-health/rahbar-outstanding-discovery-2012.html (Accessed 4.9.2013)
10. Available from: URL: http://www.ncbi.nlm.nih.gov/pubmed/?term=rahbar+s (Accessed 4.9.2013)