An Interview with Professor Sohan Singh Hayreh

Entrevista com Professor Sohan Singh Hayreh

António Campos, MD, PhD.[1,2] Sohan Singh Hayreh, MD, MS, PhD, DSc, FRCS, FRCOphth (Hon)[3]

[1] Serviço de Oftalmologia, Centro Hospitalar de Leiria, Leiria, Portugal
[2] ciTechCare, Center for Innovative Care and Health Technology, Instituto Politécnico de Leiria, Leiria, Portugal.
[3] Professor Emeritus of Ophthalmology & Director Ocular Vascular Clinic, Department of Ophthalmology & Visual Sciences, College of Medicine, University of Iowa, Iowa City, Iowa, USA

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ABSTRACT

It is an honor and an enormous privilege to be able to present Professor Sohan Singh Hayreh, rightly considered "A living legend of Ophthalmology".

As will be evident to those who read the interview, he is someone who has developed intense medical and surgical activity and has raised several clinical research laboratories from scratch. His activity was developed on three continents, thanks to an enormous capacity for change, sacrifice and refusal of the status quo.

Author of more than 450 articles and 50 book chapters, he received significant recognition and applause from the Association for Research in Vision and Ophthalmology, American Academy of Ophthalmology, Royal College of Ophthalmologists and International Society for Eye Research.

(Q): Winning the Beit fellowship was probably the greatest turn in your life, because that took you to Britain to work with Sir Duke-Elder. You didn't go with empty hands, because you already had in mind the project to work on: "the pathogenesis of optic disk edema in raised intracranial pressure". You wrote to Duke-Elder and he wrote back to you. You even state that he helped you several times, even in how to write simpler and more clear. Would you tell us some extra words on the famous Sir Duke-Elder, whom we know only from his books of Ophthalmology?

(A): Sir Stewart Duke-Elder founded the Institute of Ophthalmology, University of London in 1948, and was its first director. He was one of the most famous persons in international ophthalmology at that time. At the Institute, he recruited a team of excellent research staff; so, at that time it was the best ophthalmic research institute in the world. He had a phenomenal memory, which is highly uncommon, and most importantly one never had to go and remind him about something one had already talked about to him – I found this an extremely rare and admirable quality, among all the persons I have dealt with in my working life.

Of course I was in awe of him, but to me, Sir Stewart was not only very charming, pleasant, and kind, but also extremely generous with his time. He gave me all possible facilities and complete freedom to pursue my research plans dealing with the "Pathogenesis of optic disc edema in raised intracranial pressure", without any interference. He never told me what I should be doing, but was always ready to give advice, if I needed it. He was also totally honest in his advice. For example, when there is optic disc edema, there is always engorgement of the retinal veins, which implies that there is a rise of pressure in the retinal veins. In the monkeys, where I had experimentally produced raised intracranial pressure and optic disc edema, I wanted to measure the retinal venous pressure. In 1927, Sir Stewart had published, in the Journal of Physiology, how he did that, and that paper is still cited. So I asked him about how he did it. He smiled. He said that in 1927 he was young researcher, with a lot of juvenile enthusiasm; but now looking back, he

did not know what he was actually measuring! So, he advised me not to waste my time doing that. Sir Stewart took the time and trouble to go over my early papers with me, correcting and explaining. He had a wonderful command of the English language, and his writings were always simple, lucid and elegant, as is evident from his large seven-volumes "Textbook of Ophthalmology", and later on the 15-volume "Systems of Ophthalmology".

In short, Sir Stewart Duke-Elder played a crucial role in my ophthalmic career and indirectly in my life; I am what I am professionally because of his help. He never gave even the slightest hint that he deserved my gratitude – that is where his greatness lay. I am so much indebted to him for all his help.

Q: Your experiments with vascular casts to determine optic nerve perfusion and an inflated intracranial balloon to simulate a tumor with increasing intracranial pressure were really fine ideas for research. Nevertheless, sometimes we need physical conditions and human resources to materialize fine ideas. Would you please tell us a few words on the lab environment back then?

A: The two groups of studies you mention were done at two different institutions – the first in India and the second in London.

In 1955, when I was a Captain in the Indian Army Medical Corp, I decided to leave the army to pursue an academic and research career. A new Medical College in my home state Punjab, in India, had just opened, and it still had one very junior vacancy available, in the Anatomy department – I took that; "beggars can't be choosers". It was only one year old, an ordinary Anatomy Department, primarily involved in teaching medical students; it had no research laboratory or facilities or research funding, no research technician, and no one did any research there. I had juvenile enthusiasm to do research, but had no knowledge whatsoever about what is involved in it. As it was an anatomy department, I decided to investigate the blood supply of the eye, orbit and optic nerve.

First, I had to review the literature to learn how people had done such studies in the past. I found that one has to prepare vascular casts to study blood vessels. Then, I had to go through a good deal of trial and error to find out, finally, that liquid latex was the ideal material for vascular cast preparation. The only supplier of the liquid latex at that time was the Du Pont Company in the USA; so I wrote to them and asked, "Could you please supply me a free sample, since I cannot afford to buy it, because my salary is only $20 per month"; they very kindly supplied that. That enabled me to prepare the vascular casts, and study the ocular, optic nerve and orbital vessels. I also did related histological studies – since there was no technical help, first I had to learn histological techniques, and then I did all those histological studies myself. All this made me a good laboratory technician also!!

In 1961, after I had finished these anatomical vascular studies; I found that I had no further opportunity to do worthwhile research there for lack of facilities. In desperation, I applied for the Beit Memorial Research Fellow for Medical Research at the University of London, to investigate the "Pathogenesis of optic disc edema in raised intracranial pressure"; this topic had been an enigma since 1853, in spite of research on it by many famous neurologists and ophthalmologist; there were more than a dozen conflicting theories, but no final proof.

The Beit Fellowship was an exclusive and highly prestigious research fellowship; the majority of the previous Beit fellows had become international authorities in their medical subjects, and, at that time 3 (later six) former Beit fellows had gone on to win Nobel Prizes in Medicine. No one from India had ever been awarded that fellowship. So, I applied, with tremendous trepidation and hesitation; it was a bold, desperate step, to apply for such a high-status fellowship, because I was a totally unknown person, working in an obscure institute in India. But it was a chance – so I took it. To my utter surprise, I was selected. When I heard the news, I wrote to Sir Stewart Duke-Elder for suggestions; because he had originally agreed to be my research director and provide research facilities, if I got the fellowship. He wrote this to me: "the best thing you could do in the meantime is to read up the enormous literature on papilloedema; most of it old, for, unfortunately, for ophthalmology, nothing of importance has emerged lately. In a way that is fortunate for you, and we are looking forwards to your solving a very important problem." (And I did solve it, because my studies showed that it was due to axoplasmic flow stasis caused by raised intracranial pressure.)

This study was done at the Institute of Ophthalmology, University of London. I felt the first essential was to produce experimentally raised intracranial pressure and optic disc edema in the monkeys. That had never been done before; there was no information in the literature about how to. I devised my balloon method, with the help of the workshop in the Institute, to simulate slowly growing brain tumor and produce raised intracranial pressure.

Q: After discovering that optic disc edema in raised intracranial pressure is a consequence of the axoplasmic flow stasis, as Duke-Elder predicted you would, you decided to stay in Britain. And at the age of 37 you chose to undertake local clinical training in a context where everybody else was a lot younger than you. Please tell us some words of your daily life experience, being a foreigner and the eldest in residency.

A: Why did I start from the bottom of the totem pole in clinical ophthalmology at the age 37, having already had the highly prestigious Beit research Fellowship and many research publications? Because I found that for an in-depth clinico-etiological understanding, and scientific management of a disease, I needed to have not only research knowledge but also good clinical knowledge. I was originally trained in general surgery and I did that in the Army. Now, I wanted to be a clinical scientist in ophthalmology. There were very heavy odds against my achieving that – I needed to have a Residency in ophthalmology and pass two examinations for the Fellowship of the Royal College of Surgeons (FRCS), (and the pass rate for FRCS was only about 25%). So I joined a Residency in Birmingham Eye Hospital, although all the other Residents were young, recent medical graduates. I had

to swallow my pride and start from the bottom, in order to achieve what I wanted. It was emotionally, professionally and physically very hard. I am sure some would have called me crazy for doing all that. For example, the famous late Professor Norman Ashton at the Institute of Ophthalmology London (your Professor Cunha Vaz was a research fellow with him in early 1960s) wanted me to join him as a colleague in his department, and advised me against what I was planning to do, because he had never seen any researcher succeed in getting an FRCS.

At the Birmingham, I stayed in a room in the hospital, worked as a Resident during the day, and took emergency call duty; in the evening and on weekends, I worked to finalize my Ph.D. thesis for the University of London, based on data collected during my 3 years' research at the Institute. I had no time left for anything else. Fortunately I was not married, but this, of course, meant that I was very lonely.

Q: Your work with fluorescein angiography reminds me the famous Portuguese investigator Egas Moniz, the pioneer of cerebral angiography (doi: 10.3389/fnana.2017.00081). Apparently you shared the same focused mind and obstinate character while pursuing your goals. Do you feel that at times obstinate people pay a price in credit or gratitude from the peers?

A: Yes, one definitely pays a heavy price. Single-minded people are often resented. Also, they have little time for social activities or friendship.

Q: At the age of 42, you moved again to Edinburgh. A smaller department with no research facilities. After being a pioneer in items as the perfusion of the optic nerve, the pathogenesis of papilloedema, the role of vascular insufficiency in glaucoma, the angiographic patterns of choroidal melanoma and radiation retinopathy, scleritis and episcleritis. What was your state of mind then, considering that you had to build everything up again from ground zero? Meeting your wife at the age of 44, must have brought you a new meaning for life.

A: To advance in my professional and academic career, I had no further opening in London at that time. I was not prepared to stay and work in a dead-end situation; therefore, I had to find a place where I had more opportunities. Fortunately, a faculty position came up in the Department of Ophthalmology at the University of Edinburgh, and I was selected as a senior faculty at the University of Edinburgh and an ophthalmic consultant at the Edinburgh Royal Infirmary. I moved there in 1969. I had to establish the entire research facility there from nothing. It was a struggle, but I received a research grant from the British Medical Research Council. Being an ophthalmic consultant at the Edinburgh Royal Infirmary also, I had to run an outpatient clinic and do surgery, as well. I was achieving my aim to be both a researcher and a clinician, but it was hard work!

With the new research facilities established in Edinburgh, I did experimental and clinical research. My experimental studies completely contradicted the widespread, prevalent concepts since 1700 about the vascular patterns of the posterior ciliary arteries and their branches, and that of the choriod. My studies, contrary to the previous concept, revealed that the posterior ciliary arteries and their branches have segmental distribution, with watershed zones, and the choriocapillaris have a lobular pattern. Those studies, for the first time, explained why inflammatory, metastatic, and degenerative lesions in the choroid are localized. Since, I discovered that the optic nerve head is supplied by the posterior ciliary artery circulation, that information also explained the segmental distribution of lesions in optic nerve head vascular disorders, i.e. anterior ischemic optic neuropathy and glaucomatous optic neuropathy.

Since there had not been any systematic investigation to determine the effects of occlusion of the vortex veins, I experimentally occluded the vortex veins in monkeys in different combinations. That provided new information on that subject. For example, those studies showed the important role played by interference with the vortex vein circulation in some of the major complications following retinal detachment surgery, particularly encircling procedures.

My clinical studies dealt with ischemic optic neuropathies, giant cell arteritis, retinal artery and vein occlusion and glaucoma; those studies changed some of their basic concepts.

There, I met my wife, who was a hospital administrator at the Edinburgh Royal Infirmary, and a Classic scholar. I married for the first time at the age 44. As well as wife, life companion and mother of our two sons, she has been my literary critic and copy editor for my publications. With her as "home manager", we have had a happy family life while I continued with my work.

Q: You moved again to the States, at the age of 45. You did it after discovering the lobular pattern of the choroid, the non-anastomotic end-terminal nature of its circulation, the watershed zones between lobules, the vortex vein system and the definition of non-arteritic and arteritic anterior optic ischemic neuropathy. With this move you took another turn in life, to another center with no research facilities. What were your first impressions on arrival? How did you find the energy for so many re-starts?

A: In 1971, I was a visiting professor at 8 of the famous eye institutes in the USA, including Iowa City. That trip provided me a very good idea about the pros and cons of the various ophthalmic departments in the USA. In 1972, I was one of the candidates for the position of head of the ophthalmology department at the University of Edinburgh, but I was not selected. So I decided to leave Edinburgh.

Over the years, I had had many offers to join various American ophthalmology departments. Based on that 1971 American trip as a visiting professor, that gave me very good knowledge about the various departments there. I was impressed by the setup at the Department of Ophthalmology at the University of Iowa in Iowa City. It was a small, very friendly, highly academic and well-known ophthalmology department in a small university city. I decided to move to Iowa City. Although it was a good clinical and academic department, it had poor research facilities. I had to establish

experimental and clinical research facilities for my research by getting two large research grants from the American National Institutes of Health.

You ask "How did you find the energy for so many re-starts?" When you have that urge to explore and achieve, it does not let you rest. I am now 93; I retired from the University in January 1999, but I am still busy with research publications, see patients in my area of expertise, provide expert opinions, and recently gave two lectures on Zoom to Argentinian ophthalmologists - all without being paid since I officially retired in 1999. I am sure many people, even some patients, think I am crazy! On my official retirement from the University of Iowa in January 1999, a message I received from the late Professor Normal Aston perhaps explains it. He wrote:

"Ever since you were awarded the highly prestigious Beit Fellowship your many contributions to our knowledge have been a beacon to us all.

Now you deserve a rest – but 'Sohan' will not let you have it – so we can look forward to even more sparklers as you, at least return to your wife and family and solve yet more ophthalmic enigmas from the dynamite of your accumulated data."

Q: Most people fight for a stable career and getting a position in an institution or place. You moved from place to place throughout your life until you finally set grounds in Iowa. What kind of necessity kept you moving on and starting all over again?

A: Yes, I have made six major moves in my life to pursue what I wanted to achieve. Each of these steps offered a new challenge; I was aware that if I did not succeed, that would a total disaster, but not to accept the challenge would leave me at a standstill, and I was not willing to accept that. That was the most important impelling factor that pushed me to succeed at each step, and I committed myself to that. Necessity is the mother of invention.

Working at all these places in three continents provided me varied experience and better understanding of human nature. I found that basically the human behavior is the same, irrespective of color, creed and nationality. There are good, wonderful and helpful persons, and also some are just the reverse. There was emotional, physical and professional struggle, stress and strain at each step, but I had no other choice if I wanted to pursue a productive research and academic career. One of my favorite quotations is from Tennyson's "Ulysses": "Yet all experience is an arch wherethrough Gleams that untraveled world."

Q: Some people say that the criterion of 10 papillary disks of non-perfusion in angiography is the cut off to separate non-ischemic from ischemic CRVO. However, neovascularization in CRVO is mainly anterior and may not be revealed by angiography. Furthermore, posterior non-perfusion may not necessarily be associated with ischemic types. Relative afferent pupillary defects, deep dark hemorrhages, visual acuity of 1/10 or less, great visual field defects and ERG alterations were related with the ischemic profile, as the association of 3 of these give a 97% chance of identifying an ischemic type. Therefore, why do you think people insist on using angiographic definitions? What is their real value?

A: As for your question: why has a ''10-disc area of retinal capillary obliteration'' on fluorescein fundus angiography invariably been considered as the gold standard to differentiate the two types of CRVO? Unfortunately, there is the phenomenon of ''bandwagon jumping''. If someone well-known and influential proposes something, without paying any attention to its scientific merit, his faithful followers start to practice and publicize that. Once that is repeated again and again at conferences and other gatherings, it gets accepted as ''well-established fact'', and becomes a gold standard.

We conducted a prospective study to find out what are the most reliable clinical criteria to differentiate ischemic from non-ischemic central retinal vein occlusion (CRVO) during the early acute phase of CRVO (see Graefe's Arch Clin Exp Ophthalmol. 228,201-217.). I used the six routine, clinical tests: functional tests (visual acuity, kinetic visual fields, RAPD, and ERG) and ophthalmoscopy and fluorescein fundus angiography. That showed that overall order of reliability of these tests to make that differentiation is as follows: RAPD is a highly reliable test in eyes with uniocular CRVO, followed closely by ERG in all cases; and the combined information from these two objective tests can make such a differentiation in almost all cases. Kinetic visual fields followed by visual acuity proved to be the next reliable parameters. Fluorescein fundus angiography, because of multiple limitations, performed much worse overall than any of the functional tests; although extensive capillary obliteration was always present in ischemic CRVO, less than 10% of non-ischemic CRVO eyes also had isolated patchy capillary obliteration. The ophthalmoscopic appearance, because it is constantly evolving, is the least reliable, most misleading parameter.

Q: There is an important group of people claiming that steroids are not useful for NA-AOIN. Contrariwise to your article in the journal of neurophthalmology (doi:10.1007/s00417-008-0805-8). However, published papers enroll small numbers (DOI: 10.1016/j.ophtha.2018.03.032), steroids are given per os in small doses and sometimes a considerable amount of time elapsed in between. This topic led you to a discussion with Mark J. Kupersmith and Neil R. Miller (Letter to Editor. J Neuro-Ophthalmol 2017; 37: 347-353). Do you think that is connected to the importance that randomized clinical trials currently have in decision making?

A: As you know, non-arteritic anterior ischemic optic neuropathy (NA-AION) is a common blinding condition. Therefore, its management has become an important and controversial issue. Neurophthalmologists firmly believe, without any scientific evidence at all or valid research study, that oral steroid therapy is not beneficial in NA-AION. In early 1970s, when I applied to the National Institutes of Health in the USA to run a multicenter clinical trial about the use of corticosteroids therapy in NA-AION, the project was rejected on the grounds that there was "no scientific ra-

tionale for corticosteroid therapy in NA-AION". Since, there was no known treatment for NA-AION, I conducted, on my own, a prospective, randomized clinical trial of steroid therapy in a cohort of 613 consecutive NA-AION patients (696 eyes), with 312 patients (364 eyes) treated with steroid therapy and 301 (332 eyes) on no treatment (see Graefes Arch Clin Exp Ophthalmol 2008;246:1029- 1046.). This study showed that NA-AION eyes, treated within 2 weeks of onset, starting with high dose systemic steroids therapy, resulted in a significantly higher probability of improvement in visual acuity (p=0.001) and visual field (p=0.005) than in the untreated group. Both visual acuity and visual fields improved up to 6 months after onset of NA-AION. I discussed in that article the scientific rationale for the beneficial effect of the steroid therapy.

Neurophthalmologists refuse to accept the findings of this study, because of the following misconceptions: (i) that neural tissues in the optic nerve head and brain respond identically to acute ischemia; (ii) that NA-AION and ischemic stroke are identical phenomena, and steroid therapy is not beneficial in stroke; Since, the morphology, blood supply, and physiology of the optic nerve head and brain are totally different, and so are the pathogeneses of NA-AION and ischemic stroke. Thus, both misconceptions are invalid. Unfortunately, clinical neuro-ophthalmologists lack in-depth understanding of these basic scientific facts. The whole subject has become a political issue rather than a scientific one. Like any political party, the members follow the directives from the party bosses. In 2017, three neuro- ophthalmology leaders (Kupersmith MJ, Miller NR, Levin LA.), none of whom has done any study at all on this topic, published an editorial in the Journal Neurophthalmol (2017;37:1-2.) to perpetuate the misconception that steroid therapy is not beneficial in NA-AION, by citing two scientifically flawed studies, and equating NA-AION and optic neuritis (which etiologically are wholly different diseases), and completely ignoring my published scientific responses contradicting misconceptions (see" Hayreh SS. Ischemic optic neuropathies – where are we now? Graefes Arch Clin Exp Ophthalmol 2013;251(8):1873-1884."). This represents the phenomenon: "do not bother me with the facts; I have made up my mind".

Q: Patients in clinical trials do not necessarily look like our daily patients (doi: 10.1111/j.1524-4733.2007.00186.x) and 'The paradox of the clinical trial is that it is the best way to assess whether an intervention works, but it is arguably the worst way to assess who will benefit from it' (doi: 10.1016/S0140-6736(98)09102-8). Do you think we should use a different approach in a disease as NA-AION, where only some patients may benefit from steroids?

A: What you say is certainly true of clinical trials dealing with intravitreal anti-VEGF and intravitreal corticosteroid therapies for treatment of macular edema in retinal vein occlusion; in those clinical trials, the injections have been given regularly at intervals of 6-8 weeks for many months or even years, which is not practical in the real world. But, that is not true at all for steroid therapy in NA-AION; this is because, in retinal vein occlusion, the macular edema lasts for years, and therefore, the treatment has to be continued for years. In NA-AION, however, by contrast, steroid therapy is needed only for about 2 months, and that can be managed easily and satisfactorily in the real world, as I did by treating all my patients as outpatients for that period. The major flaws in the cited studies finding steroid therapy not beneficial in NA-AION are that: (i) too little steroid was given, and (ii) for too short a time.

To get the proper response of steroid therapy in NA--AION, one has to understand the rationale for the therapy. In NA-AION, edema of the optic disc compresses the capillaries in the optic nerve head and that results in poor circulation and ischemia; so, the objective of steroid therapy in NA- AION is to get rid of optic disc edema as quickly as possible to improve blood flow in the optic nerve head. Natural history studies have shown that optic disc edema in NA-AION last for about 8 weeks or so. Therefore, NA--AION patients require adequate doses of steroid therapy for only that length of time, for optic disc edema to resolve completely. It is well-established that steroid therapy takes time to resolve edema; therefore, to provide adequate and proper treatment, steroid therapy has to be given for an adequate length of time and in adequate doses. There lies the basic problem with the flawed studies, which are cited all the time by neuro-ophthalmologists in support of their flawed argument that steroid therapy has no beneficial effect in NA-AION.

Q: In your article "Adventure in three worlds" in Survey Ophthalmol (1991;35:317-24.", you stated: "In Indian society, humility and deference to elders and superiors is considered basic good manners; however, when I moved to the West I soon discovered that my shyness and humility were misinterpreted as weakness and ignorance. Therefore, you had to change your attitude." Please, tell us something about that.

A: Manners vary between different countries, even in the different regions of the same country. I have found that in India, Britain and USA.

Having lived for the first 34 years of my life in India, for more than 11 years in Britain, and now for over 48 years in USA, I have had a varied experience of very different cultures and working conditions. This has given me a deep sympathy with "outsiders" of all kinds. The immigrant or member of a minority group is never wholly accepted and rarely entirely comfortable. As was said long ago (The London Magazine: September 1747; page 406): "No man willingly leaves his own country"; the emigrant pays a heavy price, particularly emotionally and psychologically, however great the benefits of life in the new country. The motive for emigrating varies from person to person; for me it was entirely the pursuit of a productive research and academic career. No one who has not experienced it can conceive of the "cultural shock" that every immigrant goes through. It is an emotionally draining experience. A person going through cultural shock, as well as coping with a foreign language, culture, probably new technologies, and no friends, can work at only a fraction of his normal capabilities and needs the understanding, kindness and help of his colleagues. And the immigrant of many years' standing, like me, finds that he no longer belongs in the

country that he left and yet will never entirely belong to the country where he now lives; he never experiences the pleasure and comfort of being "one of the boys,'' of having a place in the establishment, and understanding effortlessly all those signs and references that link people to each other. The "up-side" of this is, however, that the emigrant has a wider and deeper understanding of the world and humanity.

The other part of cultural shock for the emigrant is far more serious. Since you want to move to a country with better facilities and life, initially there is great excitement. Everything looks wonderful and new. However, after 3-6 months, that excitement starts to decline and one starts to feel homesick. By about 6-9 months that reaches the bottom. That is when people get really depressed and their working capacity starts to go down. Studies have shown that some even commit suicide. During that period, the person becomes highly critical of everything in the new country and sometimes criticizes it out loud, which can alienate the local people. Over time one realizes that no place is heaven – you have traded one set of advantages and disadvantages for another, and must make the best of things in the new culture.

I have gone into this discussion about cultural shock, because I have gone through it twice in my life, and I have witnessed that in others. I have every sympathy for people who go through that and with all who are overlooked or oppressed by others.

Q: In your article "Adventure in three worlds" in Survey Ophthalmol (1991;35:317-24.", you stated: "Among my deepest beliefs is the statement, "Magna est Veritas et Praevalebit" ("great is truth and it shall prevail"). I cannot countenance dishonest or shoddy research, prevarication or hypocrisy. I avoid politics of any nature at all costs. I am an iconoclast." Would you say that being a self-made man and getting your achievements the hard way, increased your sense of honesty and fairness?

A: I value most highly honesty, fairness, and lack of prevarication or hypocrisy. For genuine and honest research, those are the foremost essentials. It may well be that the fact that I had to learn to do research step by step by myself, and make my own way, had made me more aware of the importance of honesty and fairness, and more rigorous in my judgments.

Theoretically, the objective of publishing scientific papers is to advance scientific knowledge for the benefit of humanity; however, that is not always true. Not infrequently the primary objective of publishing articles is simply to advance one's career. Flawed studies get published because of "old-boys net" reviewers, ignorant reviewers, or politics; personal considerations supersede those of science. Based on my experience of publishing about 450 peer reviewed scientific articles, based on my studies, since 1958, and reviewing published scientific literature, I have found publishing involves fair amount of politics. I have found all that gets published is not always genuine and valid, because fraudulent and misleading articles get published all the time, resulting in misinformation, which can do serious harm and result in harmful treatments. Now, with the emergence of multiple predatory journals, whose primary objective is to make money, they publish anything and everything, without strict peer review, the situation has really become bad. Following are just 3 examples.

1. In the 1950s, a famous European eye institute published multiple papers and a book describing the discovery of a "new" "central artery of the optic nerve". Those studies were the ones which originally prompted me to investigate that artery. My examination of 100 human specimens showed NO such artery, and its existence was also not found by any subsequent study. It was simply a scientific fraud, and yet those articles got published, because the first author and the director of the department was internationally famous.

2. In 1989, a study from a famous eye institute in the USA, claiming that optic nerve sheath decompression improved visual function in NA-AION, was published on an expedited basis in a reputable ophthalmic journal, because it was thought to be an extremely important treatment for NA-AION, which had no known treatment then. Immediately after that, based on my research on NA-AION, I wrote a letter to the journal, pointing out that this procedure has no scientific rationale and could be harmful. In spite of that warning, this procedure became popular worldwide, because (i) NA-AION patients were desperate for any treatment for the visual loss, and (ii) the optic nerve sheath decompression was a lucrative procedure – an ideal combination. Finally, a multicenter, randomized, clinical trial was conducted by the United States' National Institutes of Health to assess the safety and efficacy of this surgery. The trial was soon stopped, because the study concluded that the results "indicate that optic nerve decompression surgery for NAION is not effective, may be harmful, and should be abandoned." That clinical trial confirmed what I had warned 5 years earlier in my letter to the editor, based on scientific evidence; I spent only 3-4 hours to write that letter, but the clinical trial cost millions US dollars; that shows basic sciences are the foundation of Medicine.

3. In 1995, the Central Vein Occlusion Study (CVOS) Group published in Ophthalmology a randomized clinical trial study, dealing with laser panretinal photocoagulation (PRP) in ischemic CRVO, and funded by United States' National Institutes of Health. The study was designed by retina specialists from two prestigious USA ophthalmic institutes. It advocated doing PRP in eyes with "2-o'clock iris/angle neovascularization" to prevent development of neovascular glaucoma in ischemic CRVO. That study is considered a gold standard for PRP in ischemic CRVO. The most important feature of any research study is its design, because that determines its conclusions and their validity. Based on my PRP and other studies in ischemic CRVO, I found that CVOS design had multiple serious scientific flaws, which invalidated the conclusions of the study. My comments were forwarded to the authors of CVOS for response; they agreed with me about those flaws in their study.

I could cite many similar flawed published studies. Fin-

ding such scientific flaws does not make friends!

Q: In your article "Adventure in three worlds" in Survey Ophthalmol (1991;35:317-24.", you stated: "I differ seriously with research directors, who do not think it necessary actually to do the research work themselves, and delegate it to research assistants or students, with only cursory 'supervision'. Not uncommonly the final paper is written by research assistants, and the director finally becomes the spokesman of the research. No wonder mistaken and even suspect results are produced!" What should be done to change that?

A: This needs a drastic change in thinking and set up, giving the researcher freedom to conduct and publish his/her research as an independent investigator, to be held responsible and answerable to the validity of the data. The role of the director should be only to help the investigator, if need be, but not to take credit for the research in any way. For example, Sir Stewart Duke-Elder never wanted to be an author in any of my research publications, although he provided me with all the facilities and help I needed to conduct my research.

Q: In your article "Adventure in three worlds" in Survey Ophthalmol (1991;35:317-24.", you stated: "I disapprove of retrospective studies. Information recorded on a routine visit to a busy clinic (even in the best of institutions) can be very inadequate, and extracting information from such old records is extremely conducive to wishful thinking. Often, the patients whose records are used were never seen by the investigators, nor followed systematically, and the information is derived from dubious sources, with some guesswork thrown in." Could you further comment on that? And yet, why are they accepted?

A: From that article, you have already cited the reasons why I feel that retrospective studies can be flawed. The fact such studies get published is a part of life.

Q: Often in your life, the odds were against you. It was the Beit fellowship and the examinations for the Fellowship of the Royal College of Surgeons. Yet, you insisted and you were approved. Would you call it tenacity, faith, or a combination of both?

A: A combination of tenacity, faith, and hard work, and luck, too.

Q: There were important people scoffing of your capabilities or findings. I remember the British professor who predicted that no one from India was to win a Beit fellowship, the bitterness of Jules François concerning the optic nerve artery affair and the American famous professor who said, while visiting Moorfields, that your paper distinguishing ischemic from non-ischemic CRVO should have never been accepted. As a man with a low self-esteem as you once qualified yourself, that should have been hard to take. Do you hold any bitterness when you recall those moments and people, or have you forgiven all of them?

A: These comments were based on a false sense of superiority, ignorance and arrogance. The combination of ignorance and arrogance is disastrous. I have experienced such arrogant and outrageous remarks occasionally ever since I left India. Racial discrimination explains all this. Such remarks give a transient bitterness, but there is nothing that you can do. I have proven them wrong.

Q: You stated that scientific research is rarely glamorous with only occasional joy. This seems a distressing but true statement. Perhaps that explains why people often give up after getting a position, a more stable job or finishing an academic degree. So, why do some men, such as yourself, persist in exploring the path of science? Is it passion or insatiable curiosity?

A: In spite of research being a full-time lifestyle, not glamorous, involving hard work, and not paid as much as clinical work, it is passion, insatiable curiosity, devotion, and fire in the belly which forces one to keep doing that. Research costs money and does not make any money.

Q (Dra Olinda Faria's question): Professor Sohan Hayreh has published more than 400 original peer-reviewed articles and made unequalled contributions to our knowledge especially in ocular vascular disorders. All of us are grateful for this wonderful work. What advice can you give to young researchers in Ophthalmology?

A: In Indian culture, everybody thinks it is their right to give unsolicited advice to others. That used to annoy and irritate me to no end. What one does and can do depends upon one's own aim in life, personal considerations about life, circumstances, capabilities and facilities available – all these vary from person to person. To give advice without knowing all those is simply not wise. Therefore, I do not give anyone unsolicited advice. The only thing I can say to anyone who wants to attempt research as a career is: it is not glamorous; it is a poorly paid profession; it requires hard work, passion, and devotion; and the ability to persist, even during failures. But the rewards in personal satisfaction are great.

Q (Professor Rufino Silva's question): I would like to have your perspective on how important it is for an ophthalmologist to do clinical practice and research at the same time, throughout his life.

A: I have done that, but that is not an option for all. It depends upon one's personal aptitude, interest and devotion to research, and a whole lot of circumstances. Unlike clinical work, to do serious research is a full time lifestyle and not well-paid. Sometimes I suddenly wake up from sleep with a research idea; that means that is going on in the background in the brain all the time. Also, for ophthalmologists, whose important aim in life is to make lot money and have rich life style, a research career is definitely not the right choice. I found in India, Britain and the USA that persons doing research, in spite of tremendous fervor and hard work, are paid less than those doing clinical work, especially surgery. As I said before, research costs money, it does not make money.

Q (Professor José Cunha Vaz's question): From all of your multiple important findings, which one would you say was the most important for the advance of ophthalmology or which one did you enjoy the most?

A: It is a pleasure to hear from my old friend José, whom I have known since the early 1960s. It is a difficult for me to answer his question precisely. It is like asking a mother, which of her children is the best; for her they are all most beautiful and the best in the world. I can only list some of my studies, and let others decide which is "the most important for the advance of ophthalmology". Here are some examples.

1. Pathogenesis of optic disc edema in raised intracranial pressure: This was the great enigma since 1853, in spite of research on it by many famous neurologists and ophthalmologist since then, and there being more than a dozen theories about it. When I was selected for the Beit Research Fellowship in 1961, Sir Stewart Duke-Elder wrote me: "unfortunately, for ophthalmology, nothing of importance has emerged lately. In a way that is fortunate for you, and we are looking forward to your solving a very important problem." My studies showed that it is due to axoplasmic stasis, and that opening the optic nerve sheath in these patients relieves the disc edema and prevent loss of vision; this procedure since then has become a standard surgical procedure to relieve optic disc edema in these cases. Finally, solving this enigma for the first time after about 150 years was enormously satisfying.

2. The posterior ciliary artery, the choriod and choriocapillaris vascular bed: Since 1700, it was universally considered that this vascular bed was a continuous network with extensive anastomoses; however, that did not explain clinical lesions. My studies for the first time invalidated those concepts, showed that in vivo all these vascular beds have segmental distribution; with watershed zones between them, and choriocapillaris have a lobular pattern. These findings have completely altered our concepts about this previously ill-understood and ignored vascular bed. Those studies showed its importance, hemodynamics and clinical significance. They helped to explain why inflammatory, metastatic, and degenerative lesions in the choroid are usually localized, and the discovery of watershed zones explained their role in ischemic disorders of not only of the choroid but also of the optic nerve head. Correcting this mistaken concept dating from 1700 was rewarding.

3. Blood supply of the optic nerve head: My studies showed for the first time that it is primarily supplied by the posterior ciliary artery circulation. That has important implications and has helped to explain vascular disorders of the optic nerve head, particularly the pathogeneses of anterior ischemic optic neuropathy and glaucomatous optic neuropathy – common blinding disorders.

4. Nocturnal arterial hypotension: My studies for the first time discovered the important role played by it in anterior ischemic optic neuropathy, glaucomatous optic neuropathy and other ocular vascular occlusive disorders.

5. Central retinal vein occlusion: As you know, this is an important clinical condition, commonly considered as one clinical entity. My studies showed that it actually consisted of two distinct clinical entities: ischemic and nonischemic types, each with very different pathogeneses, clinical manifestations, prognoses, courses, complications, demographic characteristics, and managements. That information is crucial in the management of CRVO.

6. Central retinal artery occlusion: My comprehensive basic and clinical studies showed what the retinal tolerance time to acute ischemia is; what its various types are, and the natural history of visual outcome is in it. All that information is new and crucial in management of CRAO.

7. Natural history of visual outcome: In various diseases associated with visual loss, from the point of view of both patient and ophthalmologist, the most important piece of information required is about the natural history of visual outcome. This information is vital to determine if any advocated treatment modality is any better than the natural history of the disease. In prospective, large studies, I have investigated natural histories of visual outcome in anterior and posterior ischemic optic neuropathies, CRAO, CRVO, hemi-CRVO, BRVO, BRAO. Those studies provided very valuable information in the management of these disorders.

8. Ischemic optic neuropathies: Most of the basic, clinical and management knowledge is based on my studies. I gave the name "anterior ischemic optic neuropathy" to this clinical entity. I discovered the clinical entity of "posterior ischemic optic neuropathy"; as well, the beneficial role of steroid therapies in both of them.

9. Ophthalmic manifestations of malignant arterial hypotension: My comprehensive experimental studies on it showed for the first time that ophthalmic manifestations in it actually consist of three distinct clinical entities: hypertensive retinopathy, hypertensive choroidopathy and hypertensive optic neuropathy.

These studies contradicted many of the prevalent old "well-established" concepts about these clinical entities.

10. Vasogenic theory of glaucomatous optic neuropathy: Since 10th-century, raised intraocular pressure has been considered to be responsible for the development of glaucoma. My fluorescein angiographic, experimental and clinical studies, however, demonstrated that the primary factor responsible for it is vascular insufficiency in the optic nerve head.

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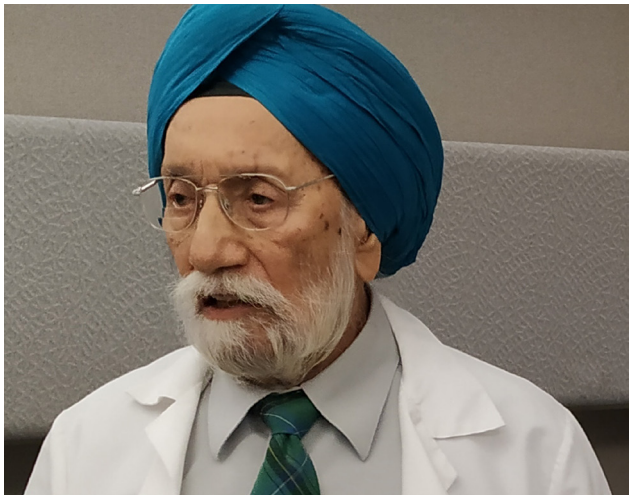

Figure 1 - Professor Sohan Singh Hayreh

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Corresponding Author/
Autor Correspondente:

António Campos
R. de Santo André
2410-197 Leiria, Portugal
acamposoft@gmail.com

Nº ORCID: 0000-0003-0490-5889