

# An Oneiropenic Account of an Ophthalmological Career

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The author has done pretty much what he wanted to do throughout his professional life. Little harm resulted. A few findings may survive.

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## 1. Introduction

To save a hapless colleague from having to write that my accomplishments are too well known to require repetition, I obtained permission from the Editor to provide a biographical introduction appropriate to a recipient of the von Sallmann Award, as long as I kept it short. I have endeavoured to comply, remembering that along with brevity 'constant digression is the saving grace of senile reminiscence' (1). To compensate for the informality of the written account of the award lecture (158), which corresponds more or less to its verbal presentation, I chose to confine this account of my professional life in the straightjacket of a conventional scientific paper.<sup>1</sup>

## 2. Materials and Methods

### *Subject*

I was born in 1922 into a middle class North London family that would nowadays be described as dysfunctional. As I remember it, my mother and father, occupying political positions on the left and right, seldom spoke to one another, nor did they have much to say to their children. The molding of my infant mind was left to my nannie, whose principal concerns were personal hygiene and the regularity of bowel movements. In order to frustrate the ambitions of my father, my object in life became to be a failure. That I am writing this piece suggests that even in this modest endeavour I was not completely successful.

I developed a scientific outlook early in life. When I started to shave, presumably around 16, I took note of a popular belief that shaving encourages the growth of hair, and decided to test it by carrying it out on just one half of my face, leaving the other as a control. Although there was little immediate effect, one side of my neck remains more hirsute than the other. Unfortunately, and I'm afraid typically, I hadn't noted down which side was treated.

As a small boy my chief interest was fighting other small boys, but before puberty I developed intellectual tastes and took to reading secretly by the light of a candle in a cupboard, when I was supposed to be asleep. When the shelf above the candle caught fire, I was discovered. The books I was reading I remember as being a text on organic chemistry and the 'Subjection of Women' by J. S. Mill. I must have been a disagreeably priggish child and even now am occasionally subject to tiresome bouts of virtue.

In fact, I never met a girl of my own age, or wished to, until I entered University at the start of World War II, and the impact had an adverse effect on my fragile work ethic and led to a mediocre degree in Physics. This was sufficient to keep me from the trenches, however, and I was recruited into an RAF research establishment where I was assigned to help develop countermeasures against German radar. Although this promised dramatic potential, in fact it involved the prosaic job of designing antennae to be carried by aircraft. This left me with small enthusiasm for electronics, and, like many others, I decided on a career in biology as a result of reading Schrödinger's book 'What Is Life?'.

Among the few post-war job opportunities that I investigated, were offers from a Dr Turing at the NPL, Dr Wilkins at King's College, and Sir Stewart Duke-Elder at University College, London, all of whose names were unknown to me. I had also written to Lord Rothschild, at Cambridge whom some source must have identified as a biologist. He could not offer a job but advised me to take whichever position had the highest salary since I had no other basis for choice. I thought one shouldn't neglect the advice of a Rothschild in these matters and thus missed the opportunity to join computer science or molecular biology when they were in their infancy. Although the quiet backwaters of ophthalmology may have been the better choice for me, I have not since permitted my personal or professional decisions be affected by financial considerations. In any case, I became a graduate student of Physiology, supported by the MRC, in the team led by Duke-Elder and Davson. This later coalesced into the Ophthalmological Research

<sup>1</sup> To avoid even the appearance of self-promotion, the numerical system of referencing has been adopted.

Group, and moved to the newly opened Institute of Ophthalmology at Judd St.

My Ph.D. training under the tutelage of Hugh Davson was rather unstructured, in the English manner. I was supposed to follow the courses in medical sciences taken by the medical and dental students, but was spotty in my attendance, so that to this day there are serious gaps in my basic knowledge. Otherwise, I was allowed to choose a topic for my thesis and then left to my own devices. After a false start in aqueous humor dynamics, I preferred to study the cornea because its less complex structure and geometry suggested the possibility of a more elegant analysis of the physical mechanisms involved. When my thesis was completed I learnt that my examiners were to be Davson and Danielli. In the U.K. these examinations were conducted in private, and Danielli started the proceedings by amiably remarking that the thesis was much too long for him to read and asking me to tell him what it was about. This took me aback since, in addition to a description of 3 years research on corneal permeability (8) and an exhaustive review of previous work on the subject (10), it contained the first and detailed proposal of the pump-leak hypothesis of corneal hydration control (8), as well as totally unrelated sections in which preliminary accounts of the interference hypothesis of corneal transparency (16) and the diffusional relationship between the aqueous and vitreous humors (18) were laid out. I suppose I was allowed to ramble on for 10 minutes before the examiners withdrew and decided I was worthy – if it had not been agreed upon beforehand.

At the insistence of my wife who wished to return to her native soil, I translocated to California in mid-career (a wise choice it later turned out, when the retirement age in the U.K. dropped to 60). While on a fellowship in San Francisco, years previously, I played tennis with several people who had since become department heads. The first to answer my telephone call when I was searching for a new job was Frank Winter from Stanford, so that is where I went. I now realize that I should have entered into protracted negotiations about space, tenure etc. but at the time these things never entered my head. Coming from the sheltered life of a research institute I had no clear concept of what a Dean represented. My transfer to Columbia, which I shall ascribe to restlessness, was negotiated in a similar informal manner.

This is probably just as well, because I could not bring much other than modest indirect costs to support a department. I have no enthusiasm for routine teaching and, after a repetition or two I begin to doubt the contents of my lecture material. Moreover, my administrative skills, although based soundly on the twin pillars of delegation and recrimination, have never been in heavy demand, I suppose principally because I lack the talent for maintaining an air of solemnity for more than a few minutes at a time. This has been a disappointment because I enjoy the social

interchange, however niggardly, that comes from committee work.

### *Experimental Methodology*

The projects referred to above were more or less self generated. Having fresh ideas has never seemed a problem; in my youth they tended to torture me as I lay in bed. If I admit to any professional failing, it is starting too many projects in moments of enthusiasm and then abandoning them. A laboratory that is advertised as providing a stimulating environment, strikes me as potentially disastrous. The NIH is wise enough to discourage this tendency by framing its grant application so that one is obliged to make a plan for three years and is not encouraged to deviate from it. Unlike many colleagues, I have enjoyed renewing my applications because it has been an opportunity to unbundle my imagination. However, Study Sections have not always been enthralled by my proposals which they sometimes have been unable to bring into focus. I suspect that the experiments buried in my old applications may be more creative than those I have carried out; I do not dare to examine whether I have achieved a single Specific Aim.

For me, selecting and clarifying the most promising projects and devising experimental plans to carry them out are the most agreeable segments of the scientific process. The actual experimentation and the analysis of the results can be tedious or exciting, in general according to whether they agree or conflict with my preconceptions. The painful part is writing the work up for publication and I have never heard any colleague admit to enjoying it. The experience of fifty years hasn't made it much easier for me, and on occasions a manuscript has been put through more than 20 revisions in an attempt to purge empty statements and useless words. I do not resent the time spent in this labor, because I believe not only is it a courtesy to one's readers to make an article as brief and clear as possible, but also because the act of forcing the sentences into a grammatical form sometimes brings to light logical deficiencies or relationships that were passed over in a superficial reading. It is dispiriting that in spite of my efforts to achieve clarity and concision, my colleagues sometimes grumble that my style is opaque, and malicious reviewers have accused me of being ungrammatical and perpetrating run-on sentences, although I confess to having no fixed system of punctuation, I deny the latter charge.

It is possible to be too fastidious. I remember when Peter Wright, (later president of the OSUK), whose intelligence was not matched by his scientific productivity, came to my lab at the Institute of Ophthalmology twice a week to work on fluorometric methods of measuring the rate of tear flow. After 2 years we had a considerable body of experimental results and sat down to write them up. As I recall it, we produced the first sentence of the Introduction but over the next

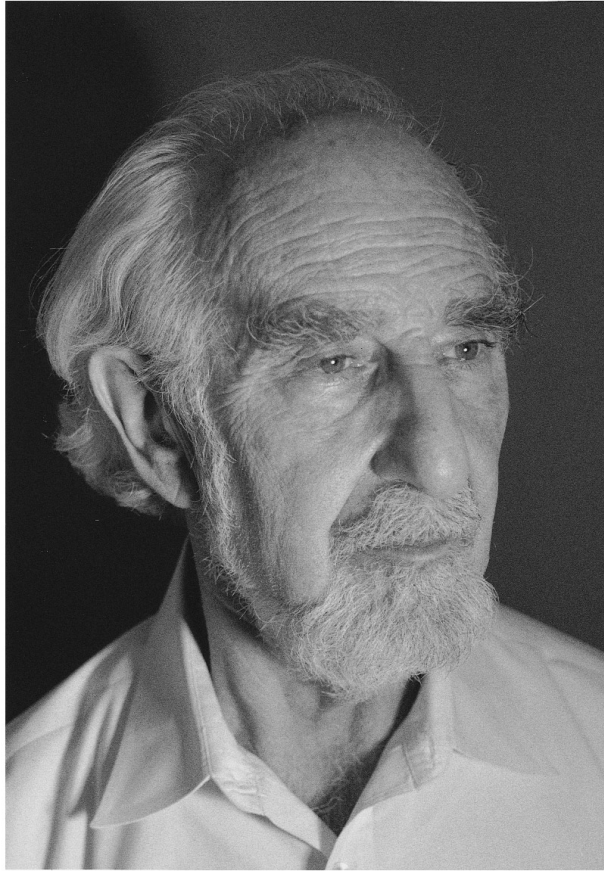


FIG. 1. The author looking askance at slovenly practices.

year or more we could never come to any agreement as to the second. Thereafter, Mishima and his colleagues published a paper (159) rendering obsolete most of what we had done; some flotsam from the disaster has been recovered (131). This may seem reminiscent of Oscar Wilde's remark that he spent the morning in taking out a comma and the afternoon in putting it back again. However, Wilde was a professional writer and I lack his facility.

On the other hand, I become quite cross (Fig. 1) over a recent phenomenon; the occasional manuscript sent for review which appears to be an unedited transcript of a preliminary dictation by the member of a team of investigators who is least fluent in English. They apparently believe that a reviewer's time is less important than their own, and he has a duty to sort out their ideas for them.

#### *Collaborative Relationships*

It can be noted that I have nearly always carried out research solo or in collaboration with one other colleague, or perhaps two. I have had the luxury of picking topics that I could believe were within the range of my skills. I may have been touched by hubris but a more direct influence was Hugh Davson. There is a distressing tendency nowadays for teams of six or more to carry out a task that seems as if it could have been performed singlehandedly. When there are more

than three authors it must be considered whether they are bringing together necessary techniques or are merely circling the wagons. It could be that strength lies not in numbers but in the weakest link of a chain.

I was raised to accept the convention that authors should be listed in alphabetical order and I have generally maintained this system when I was in control. A glance at the journals tells me that it's no longer universally applied, but I permit myself, uneasily, a minor aberration. I usually add 'except where courtesy or euphony dictate otherwise' to my admission of the habit, but the latter criterion has been invoked rarely, e.g. (5, 7, 14). On another occasion that I suggested to Professor Michaelson that the byline to a paper (37) be given a little spice by the addition of an imaginary colleague, so that it would read Maurice, Michaelson, Zauberman and Zud; he affected not to hear me, however. An amusing paper, by the way, in which I struggled to hide the absence of clean results by polished writing and by the derivation of two equations.

An exception to the general rule was Maurice and Brooks (150), which described an assay of the ocular toxicity of substances by their effect on the epithelial permeability of freshly killed mice. I thought that if the method was generally accepted it might incur the wrath of animal rightists and would allow them an easy cry of 'Ban the Brooks!' if the names were reversed, while 'Ban the Maurice!' would only sow confusion in their ranks. In fact, the method aroused no interest in industry, which is a pity because I believe it is the best single alternative to the Draize test that has been advanced.

### 3. Results

#### *Publication Mass*

The outcome of this activity has been expressed in numerous papers of variable degrees of substance, a dozen book chapters, and a handful of abstracts of original ideas that were never carried through to full publication (2–158). Most fall into the categories of vegetative physiology or of pharmacokinetics and concern the movement of things from one place in the eye to another. The frequent use of fluorescent tracers for this purpose has led colour to these drab exercises.

I have also meddled in several other fields, among them: eye movement (20, 158), experimental pathology (37, 46, 115), pain (72, 74, 102, 106, 123), tissue mechanics (90, 108, 122, 140, 144), myopia (39, 60) physiological optics (5, 16, 69, 75, 114, 147) and retinal detachment (59, 101). Instrument design has been a continuing hobby and I believe I may have been the first to obtain passable images by confocal microscopy (69) and to use the technique to elucidate a biological problem (75).

Several projects have borne fruit that has been appreciated by my colleagues, and a bunch (8, 16, 27,

38, 42, 44, 61, 62) have gradually collected from 100–300 citations over the years, a borderline respectable total in the field by this dubious measure. Other fruit has just rotted on the branch, never receiving any notice, though sometimes it seemed to me to be the best of the crop. I grieve most over the neglect of two papers on the lens (35, 58), which probably came to fruition prematurely, though I prefer to believe I am the victim of a conspiracy.

Most of my papers are now little cited, if at all. It is natural that new works should supersede the old and I would be resigned to it if they described developments or improvements. This is frequently not the case, however, and presumably the newer investigators have reimaged and repeated the project without making a bona fide effort to search the literature for a challenge to their originality. I need to remind myself that this is exactly what I did when I published a treatment of anterior chamber kinetics (88) substantially the same as that of Yablonski et al. (161) which had appeared a year earlier.

I suppose that almost everyone has been irritated because one of their relevant papers has been ignored, and I can assure them that these aggravations increase continually with age as one's early work recedes into antiquity. Nearly always, I grit my teeth and forbear to comment, but I can become openly testy if an article passes over half a dozen of my works in favor of others I judge less worthy. I am aware that my career will be obliterated in time, but I am not ready for it yet.

#### *Background Noise*

Perhaps, more important than the imaginative and competent papers in evaluating someone's scientific status are the number of dull or silly ones. Anyone might occasionally have the good fortune to conceive a felicitous idea but intelligent people should manage to avoid stupidity at all times. I surely have my share of run of the mill contributions that show little originality and have boring results yet I felt to be publishable because they contained no obvious errors and made a small contribution to knowledge.

I am less likely to be aware of any blunders unless they have been exposed by colleagues, and these have been few. The one that haunts me is that identified by Hart and Farrell (160) which I made in an equation used in calculating the light scattering by collagen fibrils. This was a consequence of intellectual torpor rather than conceptual folly. Otherwise, I have not been much embarrassed because I have hedged my misjudgments with qualifications, and I will excuse detailing these on the grounds of brevity.

#### *Negative Findings*

Many projects did not get recorded because they turned out to be misguided after a few experiments or when they were subjected to the analysis that the

preparation of an article requires. Worse than these are some truly dumb activities I have perpetrated. During my 50 years in the field, I must have used my eyes in experiments on well over 1000 occasions. Nearly always they have been free of risk, but two stand out as being criminally rash, committed while my mind was racing but apparently with a slipping clutch. One took place during the preparation of a grant application on corneal sensation, when it occurred to me one evening that it might be possible to determine the depth of pain receptors beneath the surface by establishing if there was a time lag between the contact of an irritating solution with the eye (by projecting a microdrop onto the cornea) and a feeling of pain. I chose to immediately test this with NaOH in pH steps of 0.5, in anticipation of a disagreeable sensation around pH 10. I can report that it is first felt, intensely, about 2 pH units higher, and appears to be instantaneous with the arrival of the drop; the inflammatory response last several days, however.

The other experiment that lives in my memory is when I was the subject in an evaluation of the CO<sub>2</sub> laser as a means of measuring corneal sensitivity (123), in collaboration with the late N. Brennan, of Australia. I will only comment that the fascinating optical effects I was noting should have been a warning that this was not a wise approach to tracking the recovery of sensation in an anesthetized eye. With my vision yet unimpaired, I can recognize that a little paperwork before a human or animal experiment is not a bad thing.

## **4. Discussion**

### *Social Consequences*

The question can be asked whether any significant beneficial impact on society has followed from my efforts or would it have been better if I had assisted people's vision by working as an optometrist and the governments that supported me had spent the money in funding an experimental theatre company or building a small tank.

My direct contributions to clinical ophthalmology have been few. As diagnostic tools: the specular microscope (44), conjunctival impression cytology (77) and the theory of a variety of fluorescence techniques (38, 42, 43, 55, 126, 127, 129, 156). I am unable to judge whether any patient's vision has improved as a result of their application. The simplest and possibly most powerful procedure among them has so far been neglected (127). Potentially valuable therapeutic procedures that I introduced are the transplantation of cultured corneal endothelium (83, 86) and the long term treatment of corneal pain with diluted topical anaesthetics (102). I hope that a more rational application of drugs may ultimately result from my pharmacokinetic studies (114).

Even more of a problem is to estimate any influence

of findings in basic research which often are placed like unattached fragments of a jigsaw puzzle within an incomplete picture frame. With good will, an occasional direct link can be discerned, as in the care afforded to the corneal endothelium after its importance was recognized (7, 8, 29, 30). I can allow myself to dream, with even less conviction, that remoter influences exist, for example, the awareness of a fluid suction in the stroma (32) could provide a theoretical underpinning to surgeons when they allow a corneal flap to adhere, unsutured, on its bed after keratoplasty.

#### *Private Satisfactions*

The main reward of scientific discovery is aesthetic, however, and I can estimate the pleasure that this could arouse in others only from that which it afforded me when it was first made. As an experimentalist, most of my activity has been directed towards designing approaches and instruments that often functioned as planned, or creating models of the properties of tissues that often behaved as expected. Accounts of some of these endeavours still make a good read, but not as thrillers. The written word conceals, of course, the endless little problems that gave the mind some exercise on a daily basis but have been forgotten, like clues in a crossword puzzle. More memorable have been paradoxical findings, such as the cornea rapidly swelling when air is injected into the anterior chamber (27) or the aqueous humor flow apparently tripling when cholera toxin is injected into the vitreous (112), that provided surges of excitement, but on a little reflection could be explained by simple physical mechanisms.

Rarely, alas, an unsuspected biological response had to be thought up in order to explain an unexpected finding: recently, for example, slow distortion of the corneal stroma was invoked to account for the refractive regression after laser refractive keratectomy when tissue regrowth was found to be inadequate (155).

A few models have gained the status of theories and it is these that provide the most satisfaction. The principal example is the overall construct of the cornea in which the endothelial pump confers transparency and mechanical stability on the stroma by compressing it (94). I retain a special affection, because it was my first born, frail, and adopted by strangers, for the hypothesis that ions cross the cellular layers of the cornea through the paracellular spaces (8).

The ultimate reward is to have had my mind engaged and creativity challenged, almost on a daily basis. This is a privilege restricted to few occupations, and I must be grateful.

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