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Patterns Of Organization In The Development Of Medical Know-How: The Case Of Glaucoma Research

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Abstract

This paper focuses on the longitudinal development of the glaucoma medical specialty with a view to capture the configurations of division of labor that contributed to or followed from novel understanding of the disease. The historical background is corroborated by an analysis of collaborative scholarly research over the period 1973-2003 to illustrate how successive clinical and scientific modalities co-existed and influenced each other.

1 Scientific knowledge and medical know-how

The notion of innovation in medicine is almost mechanically associated to a battery of drugs and diagnostic tools that are employed for diagnostic, therapeutic, preventive, or experimental purposes. A number of scholars however remind us that health technologies are embedded in socio-economic contexts and that the ability to provide new or improved health-care services to the population depends crucially on organizational, entrepreneurial and institutional, other than technical, factors (Blume, 1992; Henderson, 1994; Gelijns el al, 2001; Rosenberg, 2009). The latter remark resonates squarely with the broader tenet of innovation studies whose core goal is understanding the conditions which best facilitate the accumulation and the diffusion of knowledge, and its application into a variety of contexts of use (David, 1975; Rosenberg, 1976; Nelson and Winter, 1977; Metcalfe, 1998; Antonelli, 2008). In this body of scholarly work technology is portrayed as synthesis between a body of understanding and a set of codified routines that guide the associated activities. Inherent in this approach is also the uncertainty that permeates the endeavor of both cognitive and practical discovery: borrowing from Metcalfe (2010), innovation scholars portray technology as inseparable from the limitations of human agency.

The recent spur of scholarly work on medical innovation (reviewed by Consoli and Mina, 2009) draws important insights also from the history of engineering, especially works by Constant (1980) on the turbine power and by Vincenti (1993) on aeronautics design. The appealing concept therein is that of an autonomous engineering epistemology, that is, of a body of technical knowledge not subservient or derivative of science but organized according to its own dynamics, principally that of problem-solving. Nelson (2003; with Gelijns, 2010) transliterates these concepts into the realm of medicine by arguing that traditional scientific inquire on biochemical processes offers no more than a point of reference for medical research, and that the route through to workable solutions relies mostly on the development of capabilities to testing, implementing and diffusing novel diagnostic and therapeutic techniques. In this view scientific instrumentation has a central role in that it enables replicable experimentation thus guiding emergent modalities of inquiry (De Solla Price, 1984; Rosenberg, 1992; Gelijns and Rosenberg, 1994). This strand of research marks a significant point of discontinuity with the traditional literature on health technology diffusion by arguing that successful clinical modalities are independent from advances on basic scientific understanding concerning the nature and the causes of disease (Nelson, 2003; 2008; Nightingale, 2004).

A central ingredient in the study of medical innovation pace Nelson and fellow innovation scholars is the appreciation of problem-solving as engine of knowledge growth. Paraphrasing Simon (1969), problem-solving in medicine entails pursuing clearly defined goals (e.g. cure or prevent illness) through routes that Dosi and Egidi (1991) would call ‘procedurally uncertain’. In this framework the nature of the problem, or better the assortment of problem typologies, shapes the task structure, that is, the clinical modalities toward which efforts are directed (Elstein et al, 1978). But problem-solving is also multi-dimensional whereby as some problems are solved others range into view and become new foci of innovative efforts within the broad objective to improve the efficacy of the overarching procedure. Advances in medical know-how involve hierarchic search whereby meta-problems (e.g. heart failure, blindness) set the broad goal and channel subsequent efforts in search of a solution and, possibly but not imperatively, an explanation on disease. To operationalise this concept we propose that the medical problem-solving heuristic involves the definition of meta-hypotheses, or working frameworks, that circumscribe the broad operative principles of the disease area at hand.[1] The history of medicine shows that search processes within such meta-spaces likely generates multiple sub-hypotheses, some contradicting some complementing each other, some stemming as articulation of specific features within the broader model others speculating on observations that do not fit within the prevailing meta-hypothesis. It is not infrequent that sub-hypotheses develop into meta-hypotheses once demonstrated that perceived irregularities fit into a coherent revision of disease (Rosenberg, 1990). Because ex-post selection among different paradigms is a lengthy process hypotheses and styles of practice tend to co-exist over periods before some are discarded off in the long-run, or before two hypotheses are merged into one (Elstein et al, 1978).

Given the multiplicity of dimensions that are involved problem-solving entails the interaction of heterogeneous knowledge bases. Commenting on this, Consoli and Mina (2009) propose the notion of Health Innovation Systems (HIS) as framework to articulate the technical, institutional and organizational gradients of medical innovation. Such systems are dynamic constructs comprising of gateways, that is, constellations of component organizations engaging health-related activities, and pathways, that is, mechanisms aimed at the coordination of the ecologies of competences across five dimensions[2] : (i) the body of knowledge that makes up scientific understanding of disease; (ii) the set of clinical practices that support the design of diagnostic and therapeutic interventions; (iii) the organization of industry that determines the ability to produce and supply the proposed interventions; (iv) the institutional set-up for the provision of Health-Care services to the population; (v) the instituted channels for assessing the effectiveness of patient care, and for receiving and processing the feedback stemming from the front-end. The key proviso is that the translation of novelty into the clinical realm is contingent on complementary adaptations in the other component domains[3].

It goes without saying that in their continuous evolution Health Innovation Systems generate configurations of division of labor across foci of basic and applied research such as university departments, research laboratories, units for delivery of health-care services, firms as well as hybrid types like university hospitals. The present paper focuses on this particular aspect and details patterns of inter-organizational collaborations underpinning the long-term evolution of a medical specialty. Methodologically the paper differs from other studies on medical innovation in not recounting the ‘career’ of any specific technology (see Blume, 1992) but rather in trying to capture the changing boundaries of a medical discipline as successive clinical and scientific modalities co-exist and influence each other (Pickstone, 1993). In so doing we focus on interconnected dimensions of medical problem-solving, namely: the changing sets of skills that define the glaucoma specialist profession over time; the loci of scientific collaboration that have stirred new clinical practice and new medical understanding; and, the technological complex that has emerged both as a response or as a stimulus to shifting perceptions of disease. None of these taken in isolation would suffice to account for the long-term evolution of the discipline.

The paper is structured as follows. Section 2 introduces the long-term developments of the medical glaucoma specialty. Section 3 discusses the rationale for the growth of research collaboration in general, and the growing importance of division of scientific labor between academic and non-academic organizations. The empirical analysis is presented and discussed in Section 4. Section 5 concludes and summarizes.

2 Glaucoma: the silent thief of sight

An overview

Glaucoma is a family of chronic diseases due to the degeneration of the optic nerve; its onset is asymptomatic in early stages and leads to blindness if untreated. It is the second most common cause of blindness worldwide (Tylefors et al, 1995) with an estimated global incidence of about 67 million (Source: AHAF) [4]. The causes behind glaucoma and the way in which it leads to loss of sight have not been clearly identified; glaucomatous damage can be slowed down but not reversed, and no specific preventive measures exist. To date the most significant areas of improvements concerns the classification of different forms of the disease as well as refining surgical and pharmacological interventions for very specific ends. Glaucoma makes an interesting case study in that the persistence of a particular framing – which is now unanimously judged by the ophthalmology medical community as 'only partially' correct – has been at root of much misdiagnosis and partly ineffective clinical response. The following subsections elaborate a stylized synthesis of the key milestones and of the background conditions that triggered or thwarted progress in this area. Table 1 will be used as guiding reference for this historical journey, and serves not merely as recollection of events but rather as stylized summary of the two-way interdependence between scientific and clinical knowledge.

TABLE ONE ABOUT HERE

1854-1951: Although the practice of eye surgery goes back to India in the 5th century B.C., ophthalmology became established as medical specialty in Wien only in the mid-19th century (Kansupada and Sassani, 1997). Glaucoma practice moved his first important steps thanks to the pioneering work of Albert von Graefe, an eye surgeon who in the mid 1800s reported about the beneficial effects of the then experimental surgical practice called iridetcomy, an eye incision which would became standard procedure in following years. A series of further experimentations of this kind contributed to the notion that excess Intra Ocular Pressure (IOP) of the aqueous humor was the main cause of the typical congestion of glaucomatous eyes, and that surgery could provide relief by unblocking the flow (Hulke, 1859). Before the invention of specialist tools, ophthalmologists checked ocular tension by digital palpation of the eye and inspected the fundus of the eye with a slit lamp and a lens through atropine-dilated pupil.

Back in the days of Von Graefe and until the end of the XIX Century ophthalmology was the province of surgeons who would approach clinical cases in trial-and-error fashion with minimal linkages between bedside and bench. As a matter of fact until the early 1950s both in America and elsewhere ophthalmology was taught as a part of the basic medical curriculum due to overall low prospects of specializing in what was considered an incurable disease (Liesegang et al, 2003). Moreover despite the American Ophthalmological Society being operative in 1864 as the first medical specialty organization in the US, no specialized scientific outlet existed besides the Acta of the Society's meetings (Newell, 1997). In this context the assimilation of glaucoma to hydraulic blockage and the association of its cause with the most observable symptom, excess pressure, became the guiding operational principle throughout the first half of 1900. This is a clear instance of how truth-to-nature observation (Daston and Gallison, 2007) of symptomatic evidence paves the way to a model of understanding a particular phenomenology in the absence of – or inability to perceive – contrary evidence.

The absence of a proper scientific infrastructure however was no obstacle for individual practitioners who developed a variety of scientific instruments consistent with the direction indicated by Von Graefe. A state-of-the-art glaucoma test at the turn of the century consisted in the combined use of a tonometer to measure IOP, an ophthalmoscope to scrutinize the fundus of the eye, and a gonioscope to assess the iris angle. Clearly the style of practice was adapted to the perceived nature of the problem as no single tool within this battery would suffice to detect this elusive disease. The instruments also shaped the skills that were used by and taught to trainees, such as criteria for judging eye appearance and for performing surgical incisions; making records of clinical observations on the other hand was not widespread practice yet. In the following years these modalities would contribute to disclose remarkable irregularities across different forms of glaucoma, in its symptomatology and incidence across patients; this evidence, once combined together systematically, would usher a new scientific era for this area of medical practice.

1952-1970: the beginning of the second phase in the history of glaucoma research is marked by the first International Symposium on glaucoma in 1952. By bringing together for the first time practitioners from all over the world the event reaffirmed the collective identity of this dispersed community and promoted glaucoma to independent sub-specialty within the broad realm of ophthalmology. The symposium represents a noticeable point of discontinuity for the system of thinking of the ophthalmologic community because the articulated summary of different disease manifestations was tangible proof that the extent of its diversity was greater than had hitherto been appreciated. One of the key outcomes was the first international classification of glaucomas obtained by collating and comparing systematically evidence from different sources for the first time (Duke-Elder, 1955). As Table 1 shows from this point onwards glaucoma will no longer be considered a single disease but rather a family of eye conditions; a direct consequence of this was the partitioning of the glaucoma meta-problem into various sub-domains according to the established typologies and the associated modalities of research and practice.

At a more fundamental level the newly accepted heterogeneity of the disease raised doubts on the foundations of the IOP paradigm. This is confirmed by a stream of epidemiological studies aimed at testing the (hitherto granted) co-occurrence between ocular pressure and glaucoma. Following the pioneering steps of Hollows and Graham (1966) such studies demonstrated that IOP is only a risk factor, and that only about 10% of people with increased abnormal pressure are affected while about 25% of glaucoma patients have normal pressure levels (see Liesegang, 1996). These groundbreaking discoveries added substantive uncertainty concerning the aetiology of the disease and caused a stall within the medical scientific throughout the 1960s (Consoli and Ramlogan, 2008). Accordingly the standard ophthalmologic practices for glaucoma testing and therapy did not change much in this period except for the addition of perimetry, a technique to assess visual field based on direct collaboration between clinician and patient who is asked to report the detection of visual stimuli. Likewise little changed on the surgical front besides the emergence of the novel technique of implanting tubes in the eye to drain excess liquid. Overall, it seems safe to conclude that by the end of this second phase the glaucoma specialty had not changed much compared to the previous phase if not for deepening of the characteristics that shaped already existing therapeutic and diagnostic modalities.

1971-1991: Glaucoma research and practice enters a new era in the 1970s, propelled as it was by a spur of new ideas and ever more specialized conjectures inspired from clinical, epidemiologic and laboratory research (see Table 1). The accepted diversity of the disease prompted efforts aimed at perfecting the classification of glaucoma, thus paving the way to a variety of research directions. One approach set out to explore associations between glaucoma with other diseases, especially diabetes and heart conditions, in search of regularities that could elucidate on the aetiology. Another important branch of research stemmed from the rediscovery of intuitions that had been recorded back in the old days but that remained overseen or not understood properly; most prominent among these are the remarks made by von Graefe (1857) about the recurrence of an excavation in the optic nerve of a glaucomatous eye. This particular feature, which in modern jargon is known as 'cupping', became the focus of much attention and the key to fundamental developments between the mid 1960s and the late 1970s. As the incidence of IOP was downsized to risk factor practitioners who engaged also research focused on the linkages between eye pressure and damage in the optic nerve. This meta-hypothesis was articulated in two main directions: the mechanical theory had it that intraocular pressure exerts a force that compresses the optic nerve thus altering its functionality; the vascular theory conversely posited that high pressure damages the optic nerve by reducing the nourishment of blood supply. It is now accepted that neither theory explains how optic nerve damage occurs across different types of glaucoma, and that the effects described by either probably work in combination rather than being mutually exclusive (Geijssen, 1991). Table 1 reports also about two nascent research strands which would later lay the ground for biological and genetic approaches to glaucoma.

The proliferation of hypotheses concerning the aetiology coincides with the emergence of new instrumentation and pari passu advances in digital imaging, laser and ultrasound general-purpose techniques (Blume, 1992; Geljins and Rosenberg, 1999). In the second half of the 1970s US researchers discovered a correlation between the erosion of the optic nerve cum glaucoma and visual field loss; this contributed enormously to shift the reference model from hydraulic blockage to neuropathy (Drance, 1975). Accordingly IOP measurement progressively made room to alternative techniques such as assessment of eye structure (optic nerve) and of its functionality (visual field). This induced, first, the adoption of digital photography for qualitative assessment of the optic nerve and later of the scanning laser ophthalmoscope for quantitative assessment (Quigley, 1998; Sharp et al, 2004). At a more fundamental level embracement of indirect observation mediated by the technological devices underscores the evolving logic of diagnostics since glaucoma was no longer understood as a 'binary' but rather as progressive disease; one in which chances of detection and of effective treatment depended on the stage of the neuropathy; one in which, furthermore, the boundaries of clinical practice drifted in pursuit of the 'mechanical objectivity' (Daston and Gallison, 2007) promised by improved techniques for visual reproduction.

In this eventful phase the skill base of glaucoma specialists expanded to facilitate interaction with formerly unrelated areas of science; as Ramlogan and Consoli (2007) show, the universe of scholarly research on glaucoma mushroomed in journals on neurology, cellular biology and genetics after the mid-1990s. For what concerns the therapeutic front, in the mid-1980s Beta-Blockers become the drug of choice for patients with IOP-related glaucoma (Rafuse, 2003).

1992-2003: in the last phase of our stylized summary glaucoma research reaches out towards new shores such as genetics, cellular biology and molecular science. The onset of this was the discovery that glaucoma incidence varies significantly according to age, racial background, and family history; in short, that glaucoma is a demographically selective disease (Wadhwa and Higginbotham, 2005). This issue carries obvious political and institutional implications concerning accessibility of health-care both across and within countries, especially those with high ethnic mixes. The other relevant finding, that glaucoma tends to run in families, laid the ground for the discovery of the gene responsible for Primary Open Angle Glaucoma in the 1990s (Stone et al, 1997). Initial enthusiasms however dwindled as soon as it became clear that only 3% of cases are associated to defects in single genes, and that no single mode of inheritance adequately describes the disease. It seems that glaucoma depends not so much on a single gene but rather upon the interaction of several in combination with environmental factors (Wiggs, 2007). This is to say that despite remarkable progress in scientific understanding, translational gaps hold at bay improvements in practice and that the scenario of routine genetic screening remains remote.

Another important thread in glaucoma research follows on the path set by neuropathy studies back in the mid 1970s, in particular the discovery of erosion in the optic nerve fibers due to glaucomatous damage (Hoyt et al, 1973). The emergent diagnostic modality has progressively shifted from direct observation of the optic nerve to computerized assessments of the thickness of the optic nerve fibers (Retinal Nerve Fiber Layer, RFNL) (Sommer et al, 1984). In this new regime technologies such as Scanning Laser Polarimetry (by Laser Diagnostic Technologies, Inc.), Laser Retina Tomography (by Heidelberg Engineering, Inc.) and the Optical Coherence Tomography based on ultrasound (Zeiss-Meditec, Inc.) are used to produce quantitative measures of optic disc structure and nerve consistency and calculate indices for monitoring morphologic change due to disease progression over time (Schuman and Lemij, 2000). It is worth stressing that these forms of computerized assessments carry both benefits as well as problems; some of these are technical: for example, computerized data collection makes sense within a regime of longitudinal testing to detect disease progression in individual patients, but this particular task requires data handling skills from humans as well as compatibility across data collected at different points in time and, given the rapid pace of technical advance, by presumably different devices (Trick et al, 2006). Parallel to this stand concerns among ophthalmologists who seek to reaffirm the value of 'trained judgment' (Daston and Gallison, 2007) as dominant scientific style in which sophisticated artifacts capture but don't discern meaningfully patterns.[5]

The preceding observations underscore significant transformations in the skill base of glaucoma specialists, whose modern version is far removed from the eye surgeons of a century ago. Glaucoma specialists work in teams where traditional medical skills blend with interpersonal communication skills to engage both co-workers (ophthalmic nurses, optometrists, clinic managers, etc) and patients; in fact since age is a significant risk factor for increased ocular pressure, ageing populations account for progressively higher demand for eye treatment as well as long-term disease management skills as opposed to one-off interventions.

This phase marks also a divergence between diagnostic and therapeutic paradigms. For what concerns the drugs, despite well-reported failures beta-blockers are still the first therapy of choice for glaucoma (Rafuse, 2003); evidence about the associated side effects has ignited the search for alternative drugs which could target the specific features of the various forms of glaucoma that have been unveiled over the years. In the absence of a magic bullet even for IOP-related cases the most common solution in recent years has become the prescription of combined eye drops. To conclude, it is worth highlighting further recent enrichments of the educational matrix with the separation of medical ophthalmology (a range of laboratory activities for the study of specific eye diseases like glaucoma) from the general curriculum, as well as the establishment of neuro-ophthalmology as separate sub-specialty (Neetens, 2000).

3 Patterns of intra- and inter-organizational collaboration

The preceding sections illustrate that progress in clinical and scientific know-how on glaucoma has unfolded in additive fashion stirred by complementary meta-hypotheses and the emergence of associated modalities for diagnosis and treatment. That these changing knowledge structures are embedded in changing configurations of division of labor is a reasonable but still implicit assumption; in this section we seek to address the matter more explicitly. Before delving into the data it is important to remind briefly what an analysis of collaborative patterns adds to the broader endeavor of studying medical innovation. An important qualification of the evolutionary view of medical know-how discussed before is that the repertoire of activities and the skills embodied adapt to the task structure as the problem is analyzed and solutions are tested. The matrix of knowledge generating activities is therefore embedded in the institutional contexts from which it stems and whose direction it shapes in its further evolution; accordingly, the structure of activities that are needed for practical problem-solving embodies, albeit imperfectly, the kinds of organizations that partake this endeavor.

This paper focuses on collaborative research arrangements between organizations aimed at pooling resources for the development of new scientific knowledge (Hagedoorn et al., 2000; Ponds, 2009). Growing empirical evidence on research collaboration has attracted much attention recently (Katz and Martin, 1997; Wagner-Doebler 2001; Porter and Rafols, 2009). As a matter of fact increasing scale and heterogeneity of scientific collaboration fueled emergent approaches on new modes of knowledge production (Gibbons et al. 1994) and on the Triple-Helix model of interactions among academia, business firms and governmental organizations (Etzkowitz and Leydesdorff, 2000). In a nutshell the rationale for collaborative research can be articulated as follows: cost advantages due to the opportunity of pooling resources; economies of scope spurred on by the proliferation of new and ever-more specialized scientific fields and subfields; third, and related, the necessity to develop specialized expertise in the use of complex scientific instrumentation.

Propensity to collaborate entails important implications for the division of scientific labor. The common argument is that individual organizations, or organizations of a specific type, are generally unable to keep up with the increasing complexity of the attendant scientific fields. Research in the context of science-based industries emphasizes the growing importance of non-academic organizations in collaborative scientific research, and the emergence of inter-organizational networks as key locus of innovation (see Gambardella, 1995; Powell et al., 1996; Orsenigo et al, 2002; Orsenigo et al, 1997; Owen-Smith et al, 2002). Likewise, the matrix of knowledge generating activities in the field of medicine typically involves interactions across university departments, centers for health-care delivery and firms. Understanding the division of epistemic labor across these requires an appreciation of the nature of coordination between engineering science and technology, clinical science, biomedical science and medical practice. More than this, the key issue is accounting for how the evolution of knowledge and technology bear upon the division of labor across different types of organization.

To date only a handful of works have set out to address explicitly the changing configurations of division of labor underpinning medical research. Gelijns and Rosenberg (1999) detail the interaction between medical school clinicians and producers of health devices in shaping the industry of diagnostic tools. Subsequently Gelijns and Thier (2002) appreciate the extent to which universities' endowment of research tools and capabilities complements both traditional industry assets for undertaking research and development as well as clinical activities stemming from direct interaction with patients on the bedside; the thrust of this triangulation of expertise, it is argued, are feedbacks that accelerate knowledge generation, open up new opportunities for learning as well as fostering effective development of new technologies. In a recent appraisal of the long-term evolution of Life Sciences, Rosenberg (2009) reiterates that much progress is due to breaking down of interdisciplinary and inter-organizational barriers and the associated dynamics at the interface of scientific research and new product development.

Following up these authoritative antecedents the remainder of the paper investigates patterns of intra- and inter-organizational division of labor underpinning medical know-how on glaucoma, and addresses the following questions: which types of organizations become involved? How does their contribution change over time? And, does any typology associate to any particular topic or line of research?

4 Empirical analysis

Our review of collaborative scholarly work in the area of glaucoma combines primary sources, scientific articles, with secondary ones like formal summaries of the literature that aided the identification and classification of the published material. A short proviso is in order. Scholarly co-authorship evidences direct and intentional association between two or more (or groups of) authors; repeated observation of such interactions over time speaks to the organizational dynamics underpinning evolving scientific expertise (Orsenigo et al, 1997). Co-publications are frequently used as indicators of collaborative scientific research, sometimes inappropriately, as Katz and Martin (1997) warn; Lundberg et al. (2006) argue however that longitudinal analysis of co-authorship is a valid indicator for the type of task we set out to explore.

We consulted the ISI Thompson database for articles containing ‘glaucoma’ in the Topic field – which includes title, keywords and abstract. The initial search returned 13164 papers over the period 1945-2003 but since information is more detailed for scholarly work published in the 1970s and onwards, and since the phenomenon we are mostly interested in – multiple authorship – took off in the same period, we narrow the sample to 9361 papers published between 1973 and 2003. This was subdivided into 1599 ‘single author’ and 7832 ‘multiple authors’ articles and, using the institutional addresses of the authors as a guide, the latter further partitioned into *Intra-organizational* collaborations (papers co-authored by two or more individuals based in the same type of organization) and *Inter-organizational* collaborations (two or more individuals based in different types of organizations). Table 2 shows the cumulated frequencies of each of these categories across decades.

TABLE TWO ABOUT HERE

To discern meaningful patterns within these data all collaborative scholarly work was assigned to one of the following categories depending on the type of organization to which authors are affiliated: Research Units (RU) comprising universities and public research laboratories; Health-Care delivering Units (HC) comprise hospitals, clinics and medical centers; and Firms (FRM). The shares of collaborative research across the period displayed in Diagram 1 shows that after initial predominance of intra-organizational research (e.g. within HC and within RU) inter-organizational research grows from the early 1990s onwards; while the combination Research Units and Hospital type of organizations (RU-HC) has a relatively high presence throughout, in the late period firms' contribution increases as diagnostic technologies are integrated in the clinical modalities (see preceding section).

FIGURE ONE ABOUT HERE

Observing the ecology of organizational types carrying out scholarly work on glaucoma begs the question of who worked on what. Though it is hard to establish direct causality one may speculate that high level of co-specialization between objects and procedures of search reinforces complementarities and feedbacks in the organization of research activities (Powell et al, 1996; Orsenigo et al, 1997). Consistent with the initial idea that the nature of the problem dictates the problem-solving strategy (Simon, 1969) we expect to be able to make sense of correspondences between changing configurations of the division of labor associated to different clinical and therapeutic modalities vis-à-vis the historical backdrop outlined above. To address this matter we classified the papers according to research area by reading through all abstracts to assess the object of analysis and the method of investigation;[6] the screening produced a list of 26 topics divided in 5 macro-areas (see Tables 3-5 for details and the Appendix for a description). After having provided each paper with a unique 'topic identifier' we cross-tabulate these data with those on the collaboration types: Tables 3-5 provide a snapshot of the whole period 1973-2003 and of the two historical periods 1973-1990 and 1991-2003 discussed in the preceding section.

TABLES THREE, FOUR, FIVE ABOUT HERE

A look at the topics distribution in Table 3 shows that between 1973 and 2003 the macro-area of Diagnostics holds the lion share (35%) with leading topics such as Eye Structure and Neuropathy, overall consistent with the paradigmatic shift of glaucoma as progressive disease discussed earlier. Research on Therapy (second highest, 27%) confirms the prominence throughout the periods of clinical work carried out to develop or improve existing modalities based on surgery, drugs as well as Disease Management. The third most voluminous macro-area of scholarly research (18%) is on Experimental areas like Laboratory work, Genetics and Cellular Biology. By and large these raw numbers confirm the orientation outlined in the historical background.

Let us now break data longitudinally across two sub-periods 1973-1990 and 1991-2003 (Tables 4 and 5) and focus on topics rather than macro-areas. The Spearman rank-correlation test (r_s=0.102; p-value=0.619) offers a first hint at how research efforts distribute over time, and indicates that the priority of glaucoma research changed over time. A closer look at the data in fact suggests that on the one hand research on association with other diseases and assessment of changes in eye structure remain relevant throughout; on the other hand Laser Diagnostics, Cellular Biology, IOP and Drugs become relatively more popular to the detriment of Glaucoma classification, Vascular causes and Visual-Field Assessment. Further, we cross-analyze data to appreciate what configurations of division of labor emerge in the sample under analysis. The chi-square test ($p>0.001$) rejects the null hypothesis that the distributions of macro-areas and of organizational types in Table 3 (RU, HC, etc) are independent. A cursory look at these frequencies confirms what anticipated by Figure 1 namely that in the aggregate the bulk of research was carried out either in the clinical setting (HC), or at the interface between the latter and traditional research organizations (RU-HC); but Figure 1 shows also that cross-organizational research has become more diverse in the latter part of the period due to the growing involvement of firms in areas like drug development and diagnostic machinery.

To gain a more precise idea of the patterns of scientific specialization we use correspondence analysis, which is apt for graphical representations of multi-way categorical data (see Greenacre, 1984; 1993). The position of each element in a graph is the translation of quantitative relationships in spatial terms on a chi-squared metric (as opposed to Euclidean) space; in the resulting graph closer-to-average categories are near the origin while more heterogeneous ones are on the periphery of the Figure, and the distances among points reflect differences in their organizational-scientific profiles.[7] Accordingly, the graphical output of Figures 2 and 3 plots the structure of relations between 6 organizational types (rhomboid shape) and 26 research topics (dots) respectively for 1973-1990 (Table 4) and 1991-2003 (Table 5).

FIGURES TWO, THREE ABOUT HERE

Let us look at the Figures individually. Around the origin of Figure 2 are the most prolific types of scholarly collaboration by volume of published work, namely HC, RU (both intra-organizational) and RU-HC (inter-organizational) while the remaining (e.g. RU-HC-FRM) are remotely positioned to the left of the origin. If a given type has a very specialized profile, that is, high concentration of research on one topic it will appear on the periphery of the map, like the case of firms (FRM) on Drug development (dot 25) or HC-FRM and RU-FRM on early Cellular Biology research (dot 9). The most prolific types at the centre of the Figure hold heterogeneous research portfolios as confirmed by the clustering observed in proximity of the origin. Hospital-type organizations engage the whole therapeutic spectrum – except Drugs – (dots 21-24 and 26), some diagnostic modalities (12, 15, 17) as well as Classificatory and Epidemiology research (1-2 and 4-5); the other cluster orbiting around RU and RU-HC types includes a mix of diagnostic work (Neuropathy: dot 11; Eye Structure: 20), basic research (e.g. Intra-Ocular Pressure: 6). Interestingly some topics for which there is no prominent assignment of research work, are centrally placed like Laboratory experiments (7) and Disease Management (26) which are equidistant from either of the main clusters. One last remark concerns research areas at an infant stage such as Imaging Diagnostic (13) or basic research on Diagnostic (14) (bottom of the Figure) and Ultrasound (16) (top), all peripherally located.

Figure 3 for period 1991-2003 tells a different story. First of all, the core of the Figure is more populated due to the growing involvement of organizational types cum firms which were only peripheral in the preceding period; a second interesting feature is the lower dispersion of topics, dots in the graph. Combined together these indicate that this phase is characterized by clearer distribution of topics by type of collaboration and, thus, of division of labor. The top right quadrant is home to the largest inter-organizational type, RU-HC, and includes *clinical research* on two peculiar forms of Glaucoma, Early (dot 2) and Low-Tension (4), studies on Eye Structure (20) and two diagnostic areas, Ultrasound (16) and Visual-Field (19). In general, Diagnostic technologies (dots 15-19) are mostly in the right hand side quadrants with the exception of Nerve Fiber Layer assessment (17). Research on Eye Structure (20) is equidistant from the two large intra-organizational types RU and HC, respectively in the top- left and bottom- left quadrants. Comparing these we note that the former is the locus of *basic medical research* on General Glaucoma (1), of Epidemiology studies (5 and 6), of all Experimental work (7-10) and general research on Neuropathy (11); the bottom-left quadrant is that where Health-Care deliverers conduct *clinical work* on Acute Glaucoma (3) – which indeed requires urgent clinical treatment –, consolidated techniques involving Imaging technologies (16) or Nerve Fiber Assessment (17), all traditional surgery (22-24) and Disease Management (26). In the bottom-right quadrant is a mix of collaborative research involving Firms, specifically HC-FRM on laser diagnostic (15) and surgical (21) techniques, and RU-FRM on therapeutic research on IOP-lowering drugs (18 and 25). The most peripheral nodes, Firms alone or the mixed type RU-HC-FRM contribute relatively less to collaborative scholarly research on glaucoma.

Comparing Figures 2 and 3 suggests that diminishing dispersion together with redistribution of topics matches reasonably well the profile of the individual collaborations, for example Research Units mostly involved with basic research, as opposed to Health-Care deliverers with clinical research. Taken together these results lend support to the notion of division of (research) labor cum deeper specialization. The graphs also capture the maturation of diagnostic techniques from an experimental stage in the earlier period to being fully integrated in the clinical realm in the latter. In fact the aggregate picture of Table 3 conceals that clinical procedures that have always been in use, like Visual-Field Assessment or IOP-lowering drugs, are grouped together with modalities which have undergone an experimental phase during the time horizon under analysis – such as Laser Diagnostics or Laser Surgery. Another way of saying this is that without careful framing in the history of this discipline, data may actually conceal important aspects. Overall the dynamics extracted from the data fit the historical background outlined in the preceding section, in particular the schizophrenia of a discipline whose diagnostic know-how has reached a high degree of sophistication and of diversity opposed to a therapeutic menu still locked in the stone age of the old, and proved to be incorrect, IOP paradigm (for a commentary on this see Quigley, 2004). While scholarly research has made much headway on the operative principle of how glaucoma works by shifting the model of reference from hydraulic blockage to progressive (Eye Structure) and multifactorial (Association) neurological disease, knowledge about the aetiology still looms in the dark, as confirmed by the recent spur of experimental research. All along this process, and coherent with Nelson´s chief argument, scientific knowledge did not precede experiential know-how, if not to mislead. Rather, it was informed by it.

5 Concluding Remarks and Future Steps

This paper has been concerned with shifts in the jurisdiction of the glaucoma medical specialty. The history of this disease is a prime example of how the efficacy of scientific conjectures and of diagnostic and therapeutic avenues has been severely biased by incorrect framing and the persistence of the latter in the clinical realm. It is worth concluding with some reflections as on what this analysis adds to the existing body of work on medical innovation.

Let us suggest that, first, the paper reaffirms the dynamicity and uncertainty which Geljins et al (2001) hold at heart of the discovery process that enables improvements in diagnosing, healing and preventing human sickness. Transliterating Simon (1969) the search for solutions to medical problems is beset by substantive ignorance concerning the cause of disease as well as by procedural uncertainty as on how to tackle it. Progress in life sciences has gone through different regimes for organizing health-care. At heart of this process are the removal of cross-disciplinary barriers (Rosenberg, 2009) as well as the intensification of experimental regimes for manipulating, reproducing and evaluating physiological phenomena (Nelson, 2008; Nelson and Geljins, 2010). The correlation of these two forces, horizontal dynamism across disciplinary boundaries and vertical transmissions between basic scientific and experiential realms, has provided a major step change in the production, diffusion and use of knowledge in medicine (Consoli and Mina, 2009). The history of glaucoma shows that the major breakthrough, the shift from hydraulic blockage to neurological paradigm, stemmed from the latter force, systematic organization of experiential observation, and developed further guided by the former, the abridging of ophthalmology with other specialties which were brought to matter. More than this, the changing configurations of division of labor associated to these driving forces speak to the importance of diversity not only of types of organizations involved but also of typologies of interaction generated in the context of their collaboration. In so doing the paper adds an organizational dimension to our previous studies on glaucoma research which focused on the population of authors (Consoli and Ramlogan, 2008) and of scientific journals (Ramlogan and Consoli, 2007).

Another contribution of this paper is the extension of the remit of medical innovation beyond the limits explored so far. The history of diagnostic and therapeutic modalities for of glaucoma as well as the others mentioned here elucidate on the extent to which organizational configurations bring to bear on the effectiveness of experimental design. When successful, this translates into creating appropriate preconditions by activating the right mix of specialism and by designing regimes of ex-post transmission of newly acquired knowledge, namely clinical training. This is to suggest that the ‘career’ of individual technologies (see Blume, 1992) is underpinned by a wider universe, the medical discipline, which presents itself as the rightful phenomenon to observe. Medical discipline is both the game and the rules by which the game is played, in that it simultaneously organizes scientific knowledge and establishes parameters for the formation of scientific and professional settings, evidently involved with the specialization of work and division of knowledge. This resonates with Kuhn’s (1962) view about the structural dependence of science in relation to teaching; teaching shapes both the users of knowledge and those who will directly contribute to scientific advancement. The history presented here offers an indication of the extent to which practice and training have been crucial to the generation and transmission of knowledge.

Glaucoma is also an important reminder about the variety of models for innovation in medicine. The story recounted here is representative of a broad class of disciplines characterized by: limited understanding of the disease, which inhibits effective prevention; by some progress in the diagnostic realm where no dominant standard exist among clinical procedures; and by relative backwardness in the therapeutic front (existing drugs only cater for IOP-related cases). This combination of characteristics suggests an association between Glaucoma and some types of cancer (Pancreatic, Liver), while differing from other case studies where effective solutions and a good understanding of the aetiology have been achieved, like Cataract, Coronary Artery Disease, Orthopedic disk, L-VAD and Poliomyelitis. It is hoped that new empirical material will contribute to enrich both this notion of variety, and elucidate on the consequences for the organization of knowledge-generating activities.

One last obligatory remark concerns the way ahead. The recurrent addition of new empirical work asserting the relevance of ‘other’ dimensions within the complex universe of health-care adds to the impression that the more we learn the longer becomes the path. This, in the spirit with which this paper was written, is true to the extent that human know-how is an open system and thus bound to continual reconfiguration, just as our own understanding of the phenomena we set out to analyze. In this paper we emphasize the importance of two dimensions: the shift of boundaries across professional domains to feed current knowledge, and the organization of training to preserve the latter and create future knowledge. Our future research will concentrate on these two aspects, specifically: how the evolution of cross-disciplinary organizational settings impinges upon the matrix of medical-related activities; for what concerns the second issue we set out to investigate how medical curricula evolve in order to appreciate how the supply of skills adapts to the demand of ever more specialized activities. And, further down the line, we would seek to test systematically the extent to which medical disciplines develop in uneven fashion (Nelson, 2002). But for the time being we hope to have provided a first hint towards these new directions.

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Tables:

	1854-1951	1952-1970	1971-1990	1991-2003
Meta-hypothesis	*Intra Ocular Pressure*			
		Different types of glaucoma		
		Primary Open Angle Glaucoma Angle Closure Glaucoma Normal Tension Glaucoma Acute Glaucoma Child Glaucoma	*Progressive glaucomatous damage*	
			Neuropathy - Vascular cause - Mechanical cause	Optic Nerve Fibers erosion Cellular anomaly
			Hereditary components	Genetic mutations
			Epidemiology studies	
			Association with other diseases	
Diagnosis	*Measurement* IOP > Tonometer		Digital Tonometer Laser Ophthalmoscope	
	Observation Eye fundus > Ophthalmoscope Iris angle > Gonioscope	*Qualitative Functionality Assessment* Visual Field > Perimeter	Computerised Perimeter	
			Qualitative Structure Assessment Optic Nerve > Digital photography	*Quantitative Structure Assessment:* Retinal Nerve Fiber Layer > Scanning laser tomography Scanning Polarimeter Optical Coherence Tomography
Therapy	*IOP-lowering eye incision:* Iridectomy	Trabulectomy Drainage	Laser Iridectomy Laser Trabulectomy	
			IOP lowering drugs: Beta-Blockers	Combinations of eyedrops
				Neurochemistry
Division of labour	Isolated practitioners	Intra-organizational collaboration University + Hospital		
			Hospital + Firms; University + Firms	
Skills	Surgical Eye Palpation Direct Observation			
			Cross-disciplinary interaction	
			Indirect Observation	
				Team-working
				Patient Management
				Data Handling

Table 1: long-term clinical and scientific developments in glaucoma

	INTRA	INTER	Single-author
1973	16	10	45
	(23%)	(14%)	(63%)
1983	219	159	531
	(24%)	(17%	(58%)
1993	575	429	437
	(40%)	(30%)	(30%)
2003	2790	3635	586
	(40%)	(52%)	(8%)
Tot	**3600**	**4233**	**1599**

Table 2

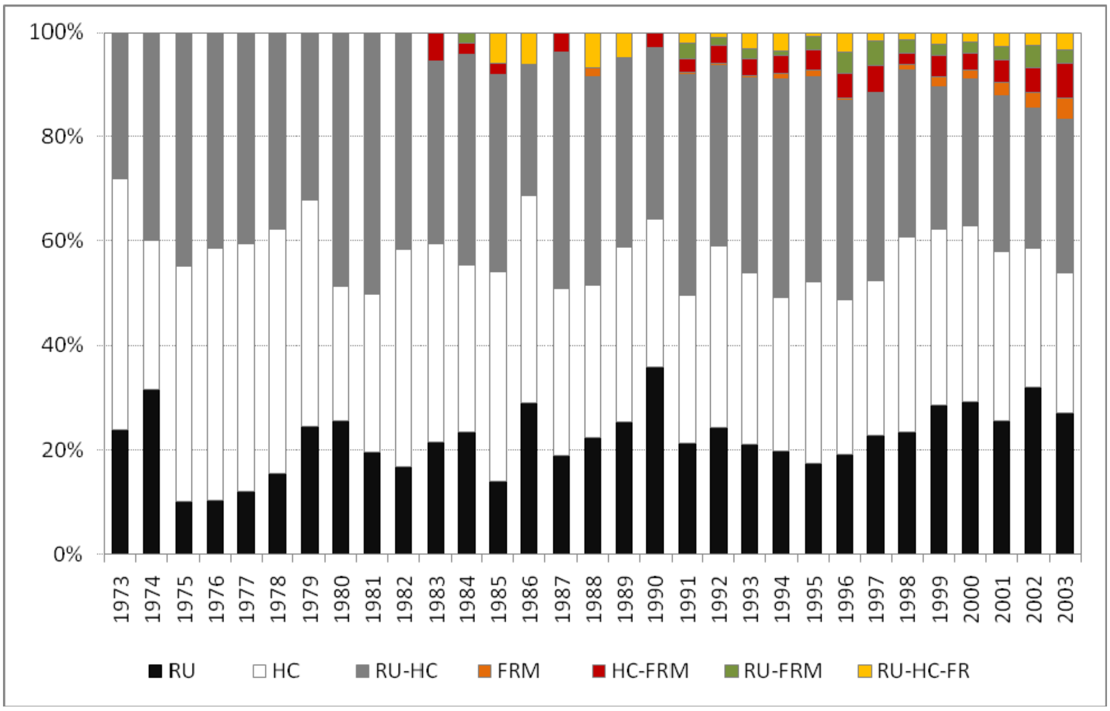

Figure 1: Collaborative scholarly research on glaucoma by type (%)

Legenda

RU = RESEARCH (UNIVERSITY DEPARTMENT + RESEARCH LABORATORY)

HC = GENERAL HOSPITAL + EYE CLINICS + ACADEMIC HEALTH CENTRES

FRM = FIRMS

	1973-2003	RU	HC	FRM	RU-HC	RU-FRM	HC-FRM	RU-HC-FR	**TOT**	**TOT Cat**
Classification	General Glaucoma	52	73	2	58	3	1	7	**196**	**580**
	Early	38	46	0	40	1	0	1	**126**	
	Acute	27	61	0	28	1	0	0	**117**	
	Low Tension	32	57	0	48	2	0	2	**141**	
Epidemiology	Association	176	302	2	221	2	10	8	**721**	**1024**
	Population	51	92	3	139	6	6	6	**303**	
Experimental	Laboratory Testing	107	142	4	135	8	15	10	**421**	**1319**
	Genetic	119	108	1	145	9	5	4	**391**	
	Cellular Biology	106	118	11	111	12	6	8	**372**	
	Molecular Biology	47	38	3	41	3	1	2	**135**	
Diagnostics	Neuropathy	124	147	3	142	6	7	3	**432**	**2779**
	Vascular	37	65	1	49	1	7	2	**162**	
	Imaging	53	39	0	41	0	0	1	**134**	
	Gen. Diagnostics	157	109	0	144	1	3	4	**418**	
	Laser Diagnostics	71	88	1	65	3	7	0	**235**	
	Ultrasound	7	21	0	8	0	0	0	**36**	
	Nerve Fiber	40	60	0	41	2	1	1	**145**	
	IOP	78	83	2	97	7	13	3	**283**	
	Visual-Field	84	78	0	122	2	4	6	**296**	
	Eye Structure	185	229	9	201	4	6	4	**638**	
Therapy	Laser Surgery	70	101	0	78	4	2	7	**262**	**2130**
	Iridectomy	61	96	0	61	0	3	1	**222**	
	Trabeculectomy	123	206	0	151	5	6	3	**494**	
	Drainage	42	85	0	67	3	3	1	**201**	
	Drugs	172	180	28	144	29	57	29	**639**	
	Disease Management	82	111	4	95	5	9	6	**312**	
	TOT	**2141**	**2735**	**74**	**2472**	**119**	**172**	**119**	**7832**	**7832**

Table 3: collaborative scholarly research on glaucoma (1973-2003)

	1973-1990	RU	HC	FRM	RU-HC	RU-FRM	HC-FRM	RU-HC-FR	**TOT**	**TOT Cat**
Classification	General Glaucoma	6	7	0	9	0	0	0	**22**	**87**
	Early	7	4	0	7	0	0	1	**19**	
	Acute	5	10	0	7	0	0	0	**22**	
	Low Tension	6	7	0	11	0	0	0	**24**	
Epidemiology	Association	14	29	0	22	0	0	2	**67**	**99**
	Population	5	12	0	15	0	0	0	**32**	
Experimental	Laboratory Testing	11	10	0	11	0	0	1	**33**	**100**
	Genetic	10	14	0	18	0	0	0	**42**	
	Cellular Biology	4	11	0	7	0	0	0	**22**	
	Molecular Biology	0	1	0	2	0	0	0	**3**	
Diagnostics	Neuropathy	12	17	0	14	1	0	0	**44**	**282**
	Vascular	7	13	0	8	0	1	0	**29**	
	Imaging	0	2	0	1	0	0	0	**3**	
	Gen. Diagnostics	4	7	0	17	0	0	0	**28**	
	Laser Diagnostics	0	2	0	0	0	0	0	**2**	
	Ultrasound	1	2	0	2	0	0	0	**5**	
	Nerve Fiber	3	4	0	1	0	0	0	**8**	
	IOP	2	5	0	7	0	1	1	**16**	
	Visual-Field	13	12	0	26	0	0	1	**52**	
	Eye Structure	23	42	0	28	0	1	1	**95**	
Therapy	Laser Surgery	9	8	0	19	0	0	0	**36**	**221**
	Iridectomy	1	4	0	6	0	0	0	**11**	
	Trabeculectomy	9	25	0	18	0	1	1	**54**	
	Drainage	4	3	0	8	0	1	0	**16**	
	Drugs	5	13	0	17	0	3	1	**39**	
	Disease Management	13	25	1	22	0	0	4	**65**	
	TOT	**174**	**289**	**1**	**303**	**1**	**8**	**13**	**789**	**789**

Table 4: collaborative scholarly research on glaucoma (1973-1990)

	1991-2003	RU	HC	FRM	RU-HC	RU-FRM	HC-FRM	RU-HC-FR	**TOT**	**TOT Cat**
Classification	General Glaucoma	46	66	2	49	3	1	7	**174**	**493**
	Early	31	42	0	33	1	0	0	**107**	
	Acute	22	51	0	21	1	0	0	**95**	
	Low Tension	26	50	0	37	2	0	2	**117**	
Epidemiology	Association	162	273	2	199	2	10	6	**654**	**925**
	Population	46	80	3	124	6	6	6	**271**	
Experimental	Laboratory Testing	96	132	4	124	8	15	9	**388**	**1219**
	Genetic	109	94	1	127	9	5	4	**349**	
	Cellular Biology	102	107	11	104	12	6	8	**350**	
	Molecular Biology	47	37	3	39	3	1	2	**132**	
Diagnostics	Neuropathy	112	130	3	128	5	7	3	**388**	**2497**
	Vascular	30	52	1	41	1	6	2	**133**	
	Imaging	53	37	0	40	0	0	1	**131**	
	Gen. Diagnostics	153	102	0	127	1	3	4	**390**	
	Laser Diagnostics	71	86	1	65	3	7	0	**233**	
	Ultrasound	6	19	0	6	0	0	0	**31**	
	Nerve Fiber	37	56	0	40	2	1	1	**137**	
	IOP	76	78	2	90	7	12	2	**267**	
	Visual-Field	71	66	0	96	2	4	5	**244**	
	Eye Structure	162	187	9	173	4	5	3	**543**	
Therapy	Laser Surgery	61	93	0	59	4	2	7	**226**	**1909**
	Iridectomy	60	92	0	55	0	3	1	**211**	
	Trabeculectomy	114	181	0	133	5	5	2	**440**	
	Drainage	38	82	0	59	3	2	1	**185**	
	Drugs	167	167	28	127	29	54	28	**600**	
	Disease Management	69	86	3	73	5	9	2	**247**	
	TOT	**1967**	**2446**	**73**	**2169**	**118**	**164**	**106**	**7043**	**7043**

Table 5: collaborative scholarly research on glaucoma (1991-2003)

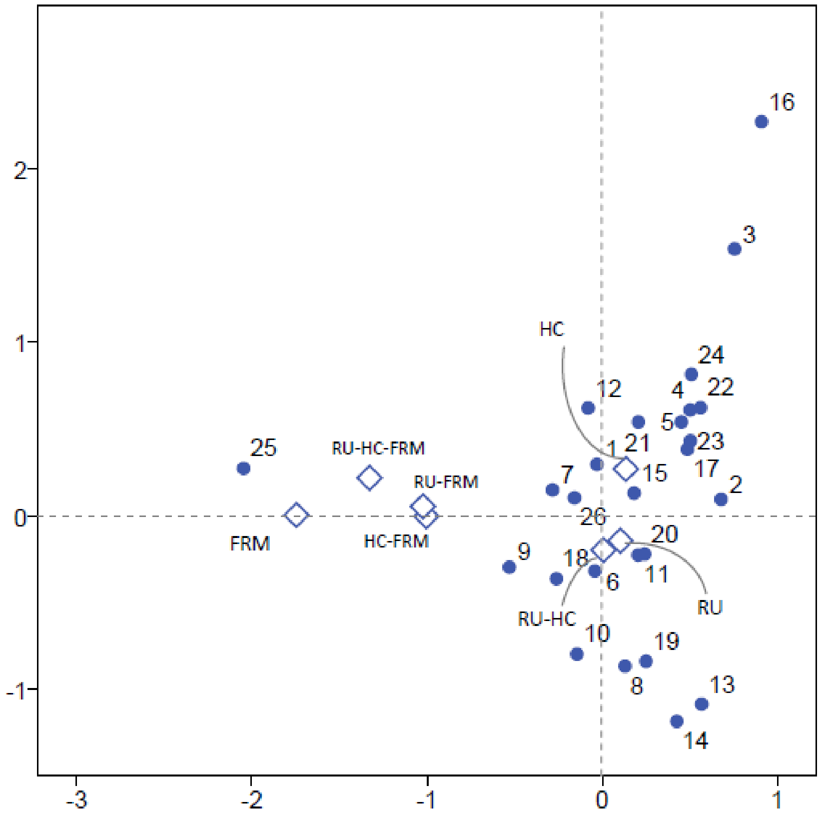

Figure 2: Correspondence Analysis 1973-1990

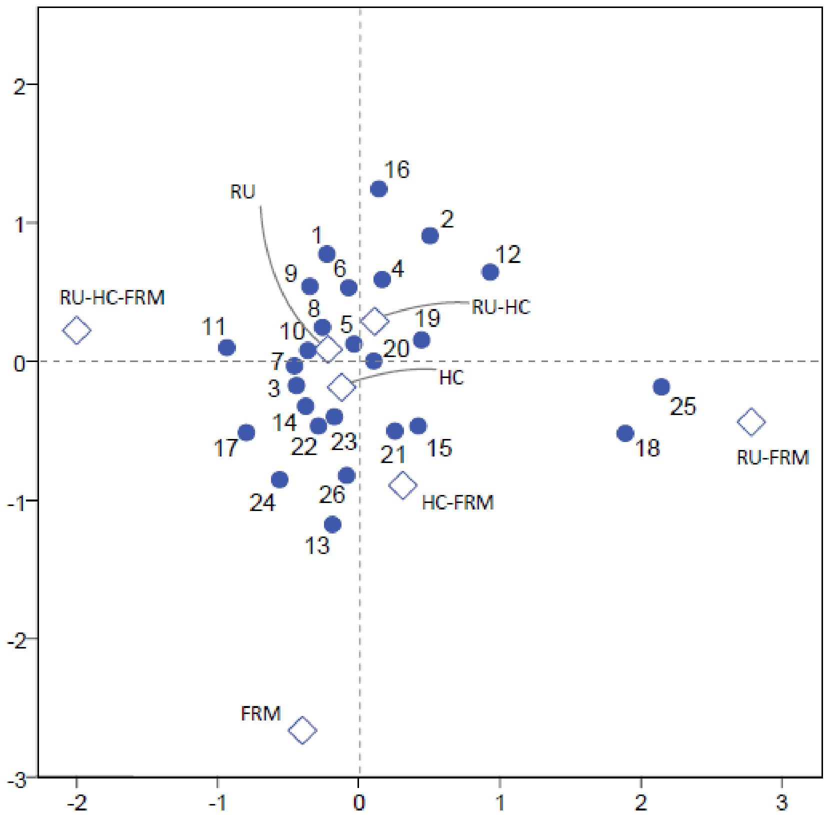

Figure 3: Correspondence Analysis 1991-2003

Appendix: Topic Identifier and coding for Correspondence Analysis

Macro-Areas	Coded Topic	Description
Classification	1. General Glaucoma	General essays; literature reviews
	2. Early	Studies on Early glaucoma
	3. Acute	Studies on Acute glaucoma
	4. Low Tension	Studies on Low-Tension glaucoma
Epidemiology	5. Association	Correlation between glaucoma and other diseases
	6. Population	Prevalence across patients by demographic group
Experimental	7. Laboratory Testing	Laboratory experiments with animals or in vitro
	8. Genetic	Studies on hereditary glaucoma and genetics
	9. Cellular Biology	Studies on the cellular functioning of glaucoma
	10. Molecular Biology	Studies on molecular processes of glaucoma
Diagnostics	11. Neuropathy	Neuropathy (damage depends on optic nerve)
	12. Vascular	Vascular theory (IOP damages optic nerve)
	13. Imaging	Reports on Imaging Technologies for glaucoma
	14. General Diagnostics	Reports on General Diagnostic techniques
	15. Laser Diagnostics	Reports on laser diagnostic devices for glaucoma
	16. Ultrasound	Reports on Ultrasound technology on glaucoma
	17. Nerve Fiber	Reports on Retinal Fiber Nerve Layer analysis
	18. IOP	Reports on Intra-Ocular Pressure measurement
	19. Visual-Field	Reports on Visual Field assessment
	20. Eye Structure	Reports on observed variations of glaucomatous eye
Therapy	21. Laser Surgery	Reports on laser surgery techniques for glaucoma
	22. Iridectomy	Reports on iris incision surgery
	23. Trabeculectomy	Reports on surgical removal of trabecular meshwork
	24. Drainage	Reports on surgical insertion of drainage device
	25. Drugs	Reports on glaucoma drug development
	26. Disease Management	Reports on long-term pharmacological treatments

[1] To fix ideas, virus theory provided the framework of reference for studies on cancer which led to the discovery of oncogenes (Kardinal and Yarbro, 1979); kinematics influenced the principles for artificial spinal disc damage (Bono and Garfin, 2004); fluid dynamics theory shaped the study of Coronary Artery Disease and inspired the principle of inserting artificial stents in the artery (Mina et al, 2007).

[2] This conceptual outline can be expanded to include more components as well as finer specifications of the existing ones; however we think that the above is inclusive enough for our purpose.

[3] Examples of indeterminacy due to lack of coordination across interdependent domains abound in studies of medical innovation. See e.g. Blume (1992) on the development of ultrasound diagnostics; Metcalfe et al (2005) on the Intra-Ocular Lens for cataract; Mina et al (2007) on the paradigm of artificial stents for Coronary Artery Disease; Yaqub (2009) on vaccines for polyomelitis; Morlacchi and Nelson (2010) on the L-VAD; Barberá et al (2010) on surgical replacement of the anatomic disc.

[4] American Health Assistance Foundation. http://www.ahaf.org/glaucoma/about/ (30 April 2010).

[5] This orientation is summarised by Weinreb (2003: 201) "With structural tests, we have to recognize that there is no perfect instrument. There wasn't one in 1994, there isn't one in 2003, and there won't be one in 2010. Every instrument, whether objective or subjective, has advantages and disadvantages."

[6] This screening was necessary because ISI only assigned a unique identifier to scientific papers by keywords after 1991. The keywords were used when they were provided in the paper; when unsure as on where to assign a paper, we downloaded and read the full publication and counted on the expertise of the various clinicians who have kindly listened and counseled us at different times in this project.

[7] Coordinates were scaled by means of canonical standardization, that is, on the basis of the relative frequencies (Gifi, 1981). The analysis was carried with SPSS software.