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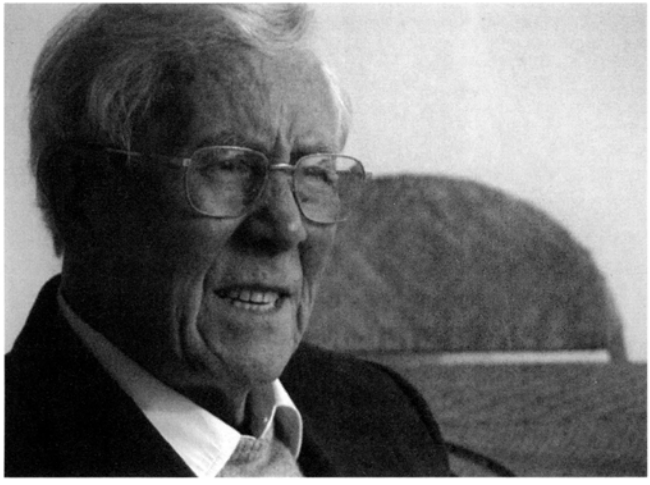

Ennio De Renzi

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Ennio De Renzi pioneered the development of neuropsychology as a scientific discipline in Italy. He carried out early work on hemispheric specialization in patients with unilateral brain lesions and made fundamental contributions to understanding the nature of virtually every neurological condition that affects higher functions: aphasia, apraxia, agnosia, amnesia, disorders of spatial cognition, and frontal lobe syndromes. In 1964 he founded the international journal Cortex and served as Editor for more than 25 years.

Ennio De Renzi

I was born in Cremona in December of 1924. Situated in Northern Italy, in the heart of the Po valley, Cremona is an agricultural center, renowned as the birthplace of such unsurpassed lute makers as Stradivari and Guarnieri. This is not, however, the greatest source of pride among its inhabitants, who instead boast of the three *T*s that characterize the city. T represents the first letter of the dialect names *turun* (a sort of nougat), *Turaz* (the 111-meter-high bell tower of the cathedral) and *tetaz* (an augmentative form pointing to the generous bosom of the Cremonese women). I can vouch for the deliciousness of *turun* and the beauty of the *Turaz*; as to the referent of the last *T*, I must have appreciated it, having been put out to a Cremonese wet nurse, but honestly I do not cherish any memory of this experience.

In those years, Italy was an apparently quiet and peaceful country that many Italians and a good few distinguished foreign statesmen (among them Winston Churchill) praised for having warded off the Reds and having at last become well-disciplined and respectful of law and order. As a matter of fact Italy was heading into the tunnel of Fascist dictatorship, from which it would emerge only 20 years later at the end of a ruinous war. A few months before my birth, Mussolini's hired killers had murdered Giacomo Matteotti, one of the opposition leaders. In the aftermath there had been a wave of protests, which had given way to a feeling of helplessness and eventually of acquiescence when in January 1925 a parliament of sheep and a pusillanimous monarchy passed the laws that wiped out any trace of political freedom. The first 20 years of my life were spent in a society ruled by a form of government that, although incomparably less bloody than those set up by the other two big dictators of the 20th century, was repressive, untruthful, and boring. Yet, in spite of the endless political jokes it inspired and the tiresome ritual of its parades, the Fascist regime was largely accepted by the middle classes, which were sensitive to the nationalist and populist topics of its propaganda: a poor country like Italy must be prepared to fight, if she wants to conquer a place at the banquet of rich countries. The atmosphere was somewhat different in my family, mainly thanks to the attitude of my father who could not stand the clownish aspects of fascism and, being a staff officer, was painfully aware of the great bluff underlying the representation of Italy as a great military power.

He used to comment upon the negative aspects of the regime with two sarcastic refrains: "fatal degenerations of tyranny," referring to the deleterious consequences of barring freedom of speech and "our doomed to defeat army," referring to the pitiful conditions of the armed forces. Yet he also harbored strong patriotic feelings and thought that he had to be present in the battlefield, where the future of his country was at stake. Consequently, I received a double-bind message and had mixed feelings about the goals pointed out by Fascist propaganda.

My decision to study medicine was neither early nor prompted by scientific interests or humanitarian aims; it came as a result of my having second thoughts. In my family there was no tradition of scientific studies. The influential figure for my cultural development was my maternal grandfather, a fine Latin scholar, who was rightly proud of being the first Italian translator of *Tacitus' Complete Works* in the modern age. When the volumes of his translation were published, a copy of them was sent to my family and was received with great respect, although I do not think it was ever actually read. He influenced my reading matter, which he guided with advice and by supplying me with 19th-century novels from both Italian and French literature (the former I found rather boring, the latter fabulous, and I learned to read them in the original language). I was an avid and precocious reader, and I still remember being angered by the skeptical smile of a family friend when, at the age of 12, I declared that I had read *Crime and Punishment* by Dostoevski. At the very least I must have understood very little of it, he commented, and I long wondered what hidden meaning of the novel I had missed and how I could find it out. At any rate, whatever the comprehension level achieved, there is no denying that my voracious reading did little to improve my performance at school, which, until the last years of "*liceo,*" was by no means outstanding, possibly due to the continuous relocations to which my father's military career obliged his family. In the early 17 years of my life, I had lived in 14 different cities and, as a result, I found it hard to establish firm relations with either teachers or classmates.

Throughout high school the sciences never really gripped me. Whether this was due to the teachers not being particularly stimulating or to my overwhelming interest in literature and history, I cannot say. Consequently, when the time came to enroll at the university, none of the scientific faculties was taken into account and I chose law. In the meantime war had broken out. Initially it seemed that its unfolding events were confined to distant parts and had a marginal impact on everyday life, but as the years went by, its threatening waves rumbled closer and came to shake our consciences with the warning of an impending catastrophe. If I try to recall my feelings in the war years, it seems that at first I was captivated by patriotic propaganda and that it was only under the pressure of events that I became progressively aware of its falsity and the abyss into which the

country was about to fall. After the Nazi occupation I had various adventures in occupied Italy and eventually reached the free part of the country where I enlisted in the Italian army that fought alongside the allies. It was in this climate of precariousness and overturning of values that I made up my mind to abandon the faculty of law, in spite of the seven examinations I had passed and to matriculate in medicine, a profession that in the wartime turmoil appeared to maintain its dignity and profile whatever the circumstances in which it was practiced. I had just read with great interest a book on the functioning of the brain and one day while talking with my father I expressed regret at not having the possibility to pursue this subject. We were taking a walk in the hills surrounding the encampment, where we were training, just before being sent to the front on the Gothic line, he as colonel and I as private. He did not miss the chance to back up the change of faculty and suggested that I enroll in law and medicine in two different universities, with the intention of keeping both doors open and of postponing the decision until the end of the war. This was a rather unlawful procedure, which, however, was very unlikely to be discovered in a period of utmost administrative chaos when Italy was split in two.

The Ghislieri and the Faculty of Medicine of Pavia

A few months later peace returned. After my discharge from the army, I finally made up my mind and took the definite decision to abandon law and to prepare for the exams of the first year of medicine: physics, chemistry, histology, and part of anatomy. I must confess that I found these matters boring and mnemonically demanding, as they indeed are, to the point that I came to miss the speculative breadth of law studies.

In the fall 1945, I passed an entrance examination to the Ghislieri College in Pavia. It was, along with the Borromeo College in Pavia and the Scuola Normale in Pisa, one of the three Italian foundations that offered deserving students from less affluent families the chance of a university education in optimal study conditions and free of charge. It was founded in the 16th century by Antonio Michele Ghislieri (1504–1572), a Dominican friar who, after having shown great zeal in fighting against heretics and infidels as Grand Inquisitor of the Holy Office (as Waldensian refugees in Calabria had come to learn at their cost during the persecution he set off against them), was elected Pope under the name of Pius V. In this capacity, he had achieved remarkable successes (as in the battle of Lepanto) as well as painful defeats, as with his decree of deposition and excommunication of Queen Elizabeth, which resulted in the worsening of the English Protestant persecution against their fellow country people. At any rate his undertaking was greatly praised by the church, which a century and half later consecrated his memory to the devotion of Catholics, making him a saint. The extent to which believers turned to Pius V's intercession to gain

heavenly protection is unknown, but surely his decision to allocate the rents of his fertile landed properties to support university students won for him the gratitude of several generations of students, who were not too overly worried by the blood and tears that the benefits they enjoyed cost. All the more as any trace of religious norms had disappeared from the college rules and all that was expected of students was that they attained good grades.

The academic year of many young men of the same age (obviously girls had not been considered as possible students by Pius V and his successors and had to wait another 20 years before being admitted to the college) began with a month devoted to "freshman re-education," a time of abuse and humiliation, to which freshmen were submitted by senior students with the declared aim of ridding them of any intellectual smugness they might harbor. This period ended with the "rain season," during which freshmen were incited to take their revenge, staging a show in which senior students were subjected to merciless jibes and put-downs. The remaining days were filled with many hours of hard work, sometimes alternating with tomfoolery and revelry and with nights spent recounting past experiences and sketching out future hopes. It is little wonder that this atmosphere fostered the beginning of deep friendships, some of which were destined to last a lifetime. I took advantage of this chance and found friends particularly among people on different courses, who gave me the opportunity to widen my cultural horizons and sharpen my wits.

Students of the early years of medicine were encouraged by the college authorities to attend laboratories and wards, even if the time spent in doing so clashed with lecture attendance, which in principle was mandatory but not actually supervised. I soon realized that good textbooks could easily make up for academic lectures. Moreover, teaching skills, as well as other mental abilities, were distributed among university professors according to a Gaussian curve, which made only few of them irreplaceable. Therefore, I attended only lectures whose content was otherwise inaccessible, e.g., those of dermatology and radiology, or those which were given by stimulating lecturers. One of them was Carlo Berlucchi, the neuropsychiatrist, who stood out from the generally dreary crowd for the meaty content of his lectures. Although not as clear as they might have been, they were the fruit of wide reading and original reflections and not the mere repetition of standard textbooks. At first hearing they could leave you with a feeling of frustration. I still remember one of them on neurosis therapy, which after having outlined the many treatments proposed, subjected each of them to radical criticism and ended up without coming to any positive recommendation. The audience was bewildered and left with the impression of being lost in a forest without a guide. It was only a few years later that I realized just how realistic a view the lecture provided of an area where the challenge was not to memorize notions of questionable validity but to assess the evidence supporting them. Berlucchi's personality and the thought-provoking

nature of his lectures piqued my old interests in the enigma of mind and led me to ask him to propose a subject for my thesis.

The Neuropsychiatric Department of Pavia

Under the influence of the German model, neurology and psychiatry were taught in one course at the undergraduate level and in one 3-year specialty at the postgraduate level. There was a certain asymmetry between the clinical importance and the scientific prestige of the two disciplines. Neurology had developed around firm anatomical and physiological notions, whereas the conceptual framework underlying the interpretation of mental disorders rested on a frailer basis. On the other hand, psychiatrists had been the first to gain autonomy from the core of medical matters and nobody would dispute their area of competence, all the more because mental patients were feared and were left willingly to their care. It had been harder for neurologists to win visibility. The most common pathology, vascular diseases, was still considered province of internal medicine and Alzheimer disease was rarely diagnosed and only in patients younger than the age of 65. In addition, there was a common and not totally unjustified belief, both among practitioners and patients, that very few effective weapons against the diseases of the nervous system had been developed and that, on the whole, neurologists' intervention was of little use. To put it bluntly, neurology provided prestige, psychiatry money.

In Pavia the Institute for Nervous and Mental Diseases was set apart from the general hospital. There were two neurological and two psychiatric wards with a total capacity of 100–150 beds. The medical staff was amazingly small: in addition to the director, Prof. Carlo Berlucchi, there were just four assistants. One of them, Prof. Gildo Gastaldi, was Berlucchi's *aiuto* (something like his deputy director) and was waiting for a competition that would earn him full professorship. The hospital could only run with the aid of the specializing doctors, who gave their services as unpaid volunteers (in actual fact they had to pay their own school fees). In those days, the exploitation of medical graduates as unpaid labor was a feature common to every clinical department and was accepted without (open) complaint. Some of these doctors also spent part of their time in research, attending the well-equipped lab of histology or those of biochemistry and clinical neurophysiology, which were still rather rudimentary, but were destined to be remarkably developed in the coming years.

Berlucchi did his rounds everyday. This was not usual practice in other clinical departments. For instance, when I attended the two main internal medicine departments, Patologia medica and Clinica medica, I never saw their chiefs in the wards discussing difficult cases with other doctors. They were hidden gods we sometimes met and greeted in the corridors, without being recognized and to whom nobody but a member of the staff would

dare raise queries. With Berlucchi it was different. First of all, every doctor could make remarks and ask questions during the round or knock on the door of his office to discuss a problem. In the latter case, it was not exceptional for him to be so engrossed by the question the person raised that he interrupted the neurological exam he was carrying out on a private patient and left the room looking for a book in the library, forgetful of the half-undressed client and his or her problems. I still remember one of them—a cousin of mine for whom I had asked a consultation—questioning me with a look of puzzlement: "Is he supposed to come back?" His approachable nature did not necessarily imply an exhaustive answer to any question, either because he was not in the mood for a pressing talk or because his reply appeared to avoid the core of the question and to address a secondary aspect of it. Eventually we realized that the gist of his comments could be hidden in an apparently irrelevant remark, maybe dissembled under the form of a bibliographic reference that we soon learned to remember and later look up in the department's well-stocked library. He had the tendency, I cannot say how much malice was involved, to declare himself poorly informed on a topic somebody had raised and to feign interest and curiosity for what was being said. It was embarrassing for the young doctor to discover after attempted explanations and much confident enthusiasm that the very same topic had already been analyzed and criticized by Berlucchi himself in one of his papers. By and large a prevalent trait of his personality was the skepticism with which he viewed the latest conceptual and therapeutic developments. He did not discourage attempts to validate them, but had probably learned throughout his career how easy it is for a novelty to kindle enthusiasm and to dull critical skills. Admittedly, some of his recurrent questions—what is the normal subject's behavior and are we sure that we are dealing with a specific effect?—were anticipating the methodological requirements that in few years would become mandatory for any research on human behavior.

Early Steps in Research

Looking back at the early years of my scientific life, I cannot help regretting that my research lacked a leading theme and jumped from one topic to another under the impulse of casual observations. In a way this is a risk inherent to clinical research, which must be ready to follow new directions suggested by observing patients. However, this flexibility must be reconciled with the need to cultivate personal lines of investigation to be pursued in depth and with tenacity. In my case, among the many subjects addressed, one looked promising. Berlucchi had remarked that our knowledge of sensory syndromes and their anatomical correlates was grounded on a relatively scanty number of cases. For instance, the evidence supporting the Déjerine-Roussy thalamic syndrome, reported by every neurological

textbook and characterized by typical pains, had actually been verified in only a few patients. In Milan, there was a home for aged poor people, which, in case of disease, also served as a hospital and was equipped with necropsy facilities. Paolo Borghi and I decided to take advantage of this opportunity and went there weekly to carry out sensory testing of stroke patients, whose names were forwarded to the necropsy service in case of death. There were many dropouts, but in 3 years we were able to collect 15 brains, albeit none of them were of patients with Déjerine-Roussy syndrome. The autopsy findings of three cases contradicted well-established notions on the vascularization and functional anatomy of the central nervous system and were worth publishing. However, we had miscalculated the energy and time we could spend in this enterprise and, when Borghi decided to become a neurosurgeon and left the department, it came to an end.

My Experience with the Rorschach Test

Eventually I found in the Rorschach test an instrument that looked promising for the assessment of psychic life and that permitted wide-ranging applications in clinical diagnosis. Different lines of psychological thought converged on the amazing idea that inkblot interpretation could open a route to understanding the human mind and character: gestalt psychology, behaviorism, and psychoanalysis. What made it particularly attractive for the study of personality traits was that their assessment no longer relied upon the examiner's insight but on objective data provided by the responses. These could be analyzed from different viewpoints (part of the inkblot selected, the role played by form, color, and movement, the content of the interpretation, etc.) and transformed into quantitative data suitable for statistical analysis. Rorschach himself had sketched the patterns of responses typical of various psychiatric disabilities, but obviously he was not familiar with the concepts of variability and probability level and it was up to the next generation to ground his intuitions on firm findings.

On this occasion I was lucky enough to avail myself of the advice of Giulio Maccacaro, a college fellow, who had just spent a year in the lab of Sir Ronald Fisher, one of the founders of modern statistics. He had acquired a good command of the discipline and was eager to divulge its principles in the medical research milieu, whose cultural backwardness in this area he knew well (the Faculty of Milan eventually rewarded his sensitivity to didactic problems by giving him the first chair of medical biometry in Italy). He was happy to accept Berlucchi's invitation to hold an elementary course in statistics at the Department of Nervous and Mental Disease and in 1953 this was indeed an event. I owe to his lessons and the discussions that followed them my understanding of the principles of inferential statistics in an era when they were generally unknown in Italy. Knowledge of this tool was of great help to me when I addressed neuropsychological issues.

In an early study on adolescent psychology, carried out with the Rorschach test, it was my impression that several of the variables underlying the responses were related to demographic factors, such as education, age, and sex. These, however, were overlooked in studies that referred to the control group's performance, which tended to be based only on university students. With Mario Isotti and Anteo Saraval we undertook the task of collecting Rorschach data from 300 normal subjects, subdivided for years of schooling, age, and sex, according to a factorial design that allowed us to weigh the influence of each factor. The analysis highlighted the import of education on performance: it increased not only the number of responses and their originality but also the percent of global, movement, color, and shade responses, i.e., those features that Rorschach had interpreted as affective life indicators. It was amazing to see how the influence of education was not confined to the development of intellectual skills but also to the wealth and variety of emotional experiences with which the subject reacted to external stimuli. This finding had implications that went beyond the scientific horizon and offered hints for reflecting on the responsibility of the ruling classes, which had so long neglected to improve the level of education of the Italian population and still made access to secondary school a privilege of middle classes.

Other research aimed at assessing the Rorschach test's contribution to the psychopathology and diagnosis of mental diseases. In one study, 105 schizophrenic patients were tested before the illness became chronic and classified into the hebephrenic, paranoid, and simple subgroups, established by Kraepelin. In a second paper, schizophrenics were compared with 70 neurotics (divided into anxious, phobic, and obsessive patients) and 50 normal subjects. Finally, in a third study, carried out with Bianca Gatti, we used the Rorschach, Rosenzweig, Minnesota, and Wechsler tests to investigate 23 subjects committed to a criminal lunatic asylum because the circumstances of their crime had led to the diagnosis of sociopathic personality. I will not go into the details of the single studies, and I will limit myself to a few general reflections on the Rorschach test's (and other projective tests') contribution to psychiatry. It was my conclusion that the additional knowledge it brought to the understanding of patients was too often meager and disappointing, especially in subjects with low education, whose poor and sometimes constrained records (as, for instance, when almost every response had anatomical content) precluded any in-depth inquiry into their personality. It is true that in a few cases one is struck by the new vistas that inkblot interpretation opens on hidden aspects of the personality, but if the time and effort required to master the test and the uncertainties that still plague its interpretation are considered, one cannot escape the question of whether they would not have been employed more fruitfully in directly interviewing patients and their families.

The Academic Power: Strengths and Weaknesses

After having attended the wards for 3 years, I obtained the specialty in nervous and mental diseases and had to make up my mind about which way to go. My preference was for staying in a hospital, possibly affiliated to a university, where clinical activity could be joined with research, while leaving the door open to an academic career. My need was also to earn a living and this was ensured by a small fellowship granted by the university on Berlucchi's recommendation and a free accommodation in the department building. Any expense beyond subsistence had to be covered by the money earned during the summer holidays, when I stood in for country doctors on leave. It was an exciting experience, because of the seemingly high earnings (at least in comparison to those to which I was accustomed) and the variety of work it offered. A minor drawback was that the area I was supposed to cover professionally was hilly with some of its country roads not asphalted and steep. This was not a real problem, if one could drive a car or a motorbike, but my only transport was a bicycle and sometimes, to get the top of the climb, I had to carry it by hand. However, what represented a persistent nightmare, which hounded me, was the risk of being called to a remote country place to assist a difficult delivery. At that time women in labor were not hospitalized systematically and the general practitioner was expected to be able to use forceps. My knowledge of obstetrics was gleaned entirely from textbooks and I still remember with a shudder the stormy night in which the midwife's shout "He's coming out" crowned with success my pushes on the woman's belly, just as her own mother was announcing that the forceps put on the fire was coming to a boil. The sigh of relief I breathed was as deep as the risk I had run of committing manslaughter.

My meager income notwithstanding, I managed to marry Rita, the woman who agreed to share her destiny and wealth with mine and who a year later gave birth to the first of my three children. She was a biologist and received from the Institute of Genetics, in which she worked, a fellowship that was as small as my own, but the consumer society was not yet in sight and we were content with what we had (along with a little help from our families).

People willing to pursue an academic career aimed for the title of *libera docenza,* inspired by the German *Privat Dozent,* which rewarded the candidate's scientific and clinical maturity. This was ascertained through the discussion of their research, a lecture on a subject drawn by lots 24 hours earlier, and the testing of clinical skills. In principle the title simply qualified the winner to give a free course to students. Actually it attested to the high level of scientific and professional know-how and was, in addition to its academic value, of benefit to its holder in two more pragmatic ways: It justified a honorarium increase in private practice and was an

appreciated qualification for head positions in general hospitals. The system had its own logic, because it indicated a career path that persuaded at least some of the most brilliant graduates to resist the lure of immediate financial gains in favor of long scientific and clinical training, with the prospect of later entering well-paid top positions. At the same time it ensured the dissemination of knowledge to hospital doctors. It did little, however, to improve university-hospital relations. A professor would be placed in the position of becoming "indebted" to people who had passed several years working in his institute with little or no remuneration and would be expected to pay them off when he chaired the board of examiners that was entrusted with the choice of head physicians. This team spirit collided with the requirements of a rigorous selection. The system was also blamed for encouraging the mere piling up of the number of papers needed to be admitted to a competition, instead of a genuine interest in research. In truth the poor selection of to-be-published articles was also due to the editorial policy of most medical journals, which was to accept papers approved by department directors, without requiring an independent evaluation by anonymous referees. The lenient selection criteria made it relatively easy to publish papers and led to an upsurge in the number of journals in print: In the 1960s, there were around 10 devoted entirely or partially to neurology. This number dropped dramatically when *libera docenza* was abolished (now we have just one national journal of neurology, although such an extreme reduction also reflects the preference to submit papers to international journals). The price we paid was that research published in Italian journals was all but ignored by the international literature, in part for linguistic reasons but also because their general standard was rather low. To remain at the periphery of the scientific community was frustrating and gave young researchers a sense of futility and a parochial view of their own work, because its aim seemed to be confined more to winning the Italian academic hierarchy's approval than to capture the interest of a wider audience of international scientists.

Veering to Neurology

I spent 6 years in Pavia, 3 in neurological and 3 in psychiatric wards. My original enthusiasm for psychiatry had waned somewhat: I still found the encounter with psychic misery emotionally involving and noetically intriguing, but was put off by the difficulties in studying it with scientific methodology. The investigation of its biological foundation was still at sea, while psychological approaches either remained at a descriptive level or set up their theoretical constructs on psychoanalytic quicksand where different phenomena are interpreted with the same repetitive formulas, which are not liable to refutation. In those years, there was also in Europe a growing interest in approaching psychiatric troubles from an

existentialist perspective, which was thought to offer more comprehensive insight into the role of humans in the world. It was not easy to follow these students' philosophical jargon and to my shame I must confess to having failed to understand what profit a doctor might gain from their speculations, however stimulating they were theoretically. As a result of these perplexities, I was slowly turning to neurology as a more promising field of investigation, although still uncertain about what subject to choose for my research.

In 1956, Prof. Gastaldi invited me to join his group in the Department of Nervous and Mental Disease of the University of Modena. I was happy to accept his offer, as I had already had the opportunity to work with him and to appreciate his acumen and the friendly and generous rapport he cultivated with his coworkers. I stayed in Modena for 1 year and in 1957 I followed Gastaldi in Milan, where he had been called to hold the Chair of Nervous and Mental Disease. Both disciplines were taught by him to medical students, but only neurological patients were hospitalized in the wards. Moreover the faculty had already called another professor just for psychiatry, thus prefiguring the separation between the two specialties that was to be formalized nationwide in a few years. These circumstances concurred to strengthen my decision to devote myself entirely to neurology. Eventually I was given a stable position along with a regular stipend, which, added to that earned by my wife as a high school science teacher, put an end to my economic worries, even though the size of my family increased (by the end of the 1960s we had three children).

Neuropsychology in the Early Sixties

The interest I developed for neuropsychology (this name became popular only later, the term we used then was "higher nervous function disorders") had been first aroused by the encounter with a few patients who presented a conspicuous impairment in the cognitive area. I still remember the amazement with which I listened to the speech of a typical Wernicke's patient, who showed a striking dissociation between her firm belief that she was communicating and the lack of meaning of her jargon. Other patients, whose behavior I spent several hours trying to define, were a patient with a post-traumatic Korsakov and an autobiographic delusion, one with spatial disorientation, and a third one with multisensory neglect. They interested me, because their conditions gave insights into the architecture of the mind, established a strong link with the brain and were hopefully less convoluted than affective disorders. Also a factor that militated in favor of carrying out research in this area was that it did not require strong financial support, which would not have been available in those days. Yet it was not easy to wade through the literature and the controversies that arose from it.

The method that prior to the First World War had provided an opportunity to gather a large body of information on how mental skills were organized in the brain was based on single-patient study of the anatomical substrate underlying the derangement of a given ability. It required a shrewd clinical investigator and the possibility of performing the autopsy. In the course of the 20th century the latter condition had become more difficult to meet, mainly because customs had evolved and relatives had become reluctant to give their consent. Also hospitalization had become shorter and it was no longer possible to keep patients in the hospital indefinitely, waiting for their death (as was the case for Broca's patient Tan-Tan who had been hospitalized for 10 years). As a result, anatomical information on the locus and extent of damage was limited almost exclusively to neurosurgical patients. Nobody would have predicted that within a few years technology would fulfill the dream harbored by generations of neuropsychologists, i.e., the *in vivo* localization of the lesion responsible for the symptom investigated. Twenty years later the question of localizing the anatomical correlates of a symptom was put between brackets by the introduction of a new method of symptom analysis, which rested entirely on the identification of cognitive modules. This approach required, however, the development of an information processing theory and the construction of cognitive models.

In the 1960s, the autopsy impasse was overcome by group studies, which had the double advantage of using a standardized method of evaluation and having criteria of localization that were not dependent on necroscopy findings. They were based on a comparison between the mental test performance of two or more groups of patients, defined on the grounds of an easily ascertainable feature, either anatomical (hemispheric side of lesion, cerebral lobe damaged) or clinical (aphasia, visual field defect). Care was taken to avoid selection biases and to have a normal control group. The tasks used were often constructed *ad hoc* with the aim of testing a specific ability and of yielding a score that could be submitted to statistical analysis. This methodology permitted active research planning and the testing of *a priori* defined hypotheses and it was no longer dependent on the chance of finding an interesting patient.

It is only fair to acknowledge that there was a turning point in this research area when its doors were opened to experimental psychologists, who brought a methodological rigor in treating psychological data that neurologists were not familiar with. In between the two World Wars there were indeed psychologists who had worked with neurologists (e.g., Gelb and Weigl worked with Goldstein in Germany) or who had developed their own line of research in the study of cognitive disorders (e.g., Weisenburg and McBride in the United States and Ombredanne in France), but their participation had been occasional and had not substantially influenced research methodology, as it did now that they were present in various centers.

Among the earliest contributions to be remembered are those of Brenda Milner from the Montreal Neurological Institute on the psychological effects of epileptic patients' temporal lobectomy and those of Hans L. Teuber and coworkers in New York on the consequence of Korean War veterans' missile cerebral injuries on a wide range of sensory and cognitive functions. Group studies were also carried out by Hécaen and coworkers at the Saint Anne Hospital in Paris predominantly in neurosurgical patients and by Oliver Zangwill and coworkers at the National Hospital in London in patients selected for the presence of a symptom rather than for the locus of lesion. With the partial exception of England, in the early postwar period European research in this area was still in the hands of neurologists. In Italy, there was only a small number of faculties of psychology and the few psychologists interested in patients were concerned mainly with those affected by psychiatric difficulties. Then the situation progressively changed and a group of young physiologists and psychologists (Berlucchi Jr., Marzi, Rizzolatti, and Umiltà) began to investigate the issue of hemispheric differences of function in normal subjects. As the number of psychology faculties increased, teachers and researchers with a solid neurobiological and neuropsychological background were in great demand and that favored the passage of neurologists to the new faculties.

Classifying patients based on the damaged lobe was not an easy task and, with few exceptions (e.g., Milner's studies), its accuracy was questionable. For instance, Teuber and coworkers were satisfied with the radiological information provided by the missile entrance holes, which were far from being waterproof. Benton and other authors preferred to group patients by the damaged hemisphere, a criterion that could be inferred directly from clinical signs (the side of motor, sensory and/or visual field deficits, language impairment, etc.) and, therefore, was ascertainable in practically every patient. The emphasis on the hemisphere dimension received impetus from Sperry and coworkers' studies on patients submitted to commissurotomy for the relief of epilepsy, which allowed them to investigate the functional competence of each hemisphere, free from the influence of the other. The rekindled interest in the issue of hemispheric dominance focused mainly on the right hemisphere, whose contribution to cognitive skills had been dismissed in the past, by being defined as "mute," but which now, if properly tested, were revealed to play a critical role in an array of mental performances.

This was the subject of my research throughout the rest of my working life. For the first decades the emphasis was on group studies. Then the pendulum swung back to single case studies, which took advantage of cognitive psychology models and the possibility of localizing the lesion *in vivo* by imaging techniques. I will not report my work in a strict chronological order to avoid a disjointed and confused narrative. I will summarize together studies that addressed the same general topic, even if they were

carried out at intervals of several years, and I will put in here and there news about my life and the academic environment.

Early Studies on Aphasia

My early studies were on aphasia and they were carried out with Luigi A. Vignolo, who had graduated in 1959 with a thesis on aphasia and had spent some time with F. Lhermitte at the Centre du Langage of La Salpétrière, in Paris. We decided to address the question of whether aphasics' comprehension deficit also involves nonverbal information, such as that transmitted by miming. We were lucky enough to have the help of the Piccolo Teatro della Città di Milano mimes, who prepared short sketches in which everyday actions (hammering a nail, putting a valise on the luggage rack of a train, etc.) were mimed. Findings were in keeping with the aphasics' impairment hypothesis and we prepared a communication for the 7th International Congress of Neurology, which was to be held in Rome and had a plenary session devoted to aphasia. There were also two free communication sessions, chaired by Hécaen and Benton, and our paper was assigned to Benton's session. We sent it to him for a preliminary screening and received warm words of encouragement, but also the query as to whether we had tested normal subjects' behavior. We had not, on the naïve assumption that it ought to have been flawless. The dialogue, which began by correspondence, went on throughout the Congress and has never stopped since. Indeed it heralded the beginning of a special lifelong friendship. Arthur Benton is now 95 years old and is still remarkably lucid. In 1964, he spent 2 months in Milan, giving a series of lectures on neuropsychology, in which the history and state-of-the-art of the main symptoms were analyzed and the methodological requisites for their investigation underlined in his own plain and persuasive manner. They were translated into Italian and published as a book that was widely read and helped rekindle attention to disorders of cognition among Italian neurologists. In 1965, I spent some time at his lab in Iowa City and then devoted the last fortnight to visiting the places where neuropsychological research was being actively pursued in the United States. There were few of them, and people were delighted to meet someone else who shared the same area of interest. Thus, I struck up a friendship with a number of colleagues.

Of all the papers I had published in those years the one on the Token test was the most resonant. What prompted its development was a paper by George Miller, which, by emphasizing how redundant verbal communication is, gave me the idea that a way to enhance the sensitivity of a sentence comprehension test to aphasic impairment was to reduce to a minimum the redundancy of its word order. By doing so, each word had to be decoded individually, no cue being available from the other components of the sentence, while the intellectual and syntactic complexity of

the message remained low. The test principles and its early findings were communicated in the first post-war joint meeting of the British and Italian neurological societies and were then published with Vignolo in *Brain*. The sensitivity and specificity of the Token test were definitely confirmed a few years later by Boller and Vignolo. They found that, although right brain-damaged patients performed as well as normal controls, the test was failed not only by left brain-damaged patients in general but also by a subgroup that had been screened for the ability to pass demanding comprehension tasks. A shortened version of the test was prepared by Faglioni and myself and given to a large normal sample, providing the correction for age and education and the score discriminating normal from pathological performance. The test was translated into many languages and gained great popularity as an aphasia severity index.

The Birth of the Milan Group

Group studies are expensive in terms of time and energy, as they often imply testing between 100 and 200 subjects, if normal controls are included. At that time, grants for research were scarcely available and I had to arrange on my own for patients to be tested. The only way was to look for coworkers among doctors specializing in neurology, asking them whether they were willing to devote to research the time they had free from clinical duties, in the knowledge that the only reward would be their name on the paper. There was never a dearth of people eager to participate and I could easily assemble a number of enthusiastic and bright young colleagues, ready to spend hours and hours in data collection and analysis and who came to be known as the Milan group. On my part I dare to credit myself for having something of a talent scout ability and the bent for fostering a relaxed and friendly atmosphere. Some of these colleagues eventually followed other routes (Mario Savoiardo and Giuseppe Scotti became neuroradiologists of some repute) or went abroad (Francois Boller); others carried on their own line of research as leaders of new groups and crowned their career becoming full professors and chiefs of neurology departments. Among them I wish to remember, in addition to Vignolo: Pietro Faglioni, Hans Spinnler, and Anna Basso. Faglioni developed a degree of interest and competence in statistics, which is rare to find among clinicians, and became our guide and expert in the use of parametric and nonparametric analyses, freeing us from the slavish dependence on standard programs. Spinnler had a tireless working capability, great critical insight, and a good command of German, a quality that unfortunately is getting rarer and rarer and that helped him (and indirectly us too) access the ancient literature, avoiding the risk of rediscovering what had already been published. Basso pioneered aphasia rehabilitation in Italy and her painstaking assessment of language disorders and their evolution was of invaluable aid to our studies. The bond

with these colleagues soon went beyond professional interactions and took on all the features of friendship, also fostered by the many cultural and political interests we shared.

Apraxia

Ideomotor Apraxia

The next subject I investigated was ideomotor apraxia (IMA), a disruption of gesture execution, which Liepmann had identified as an autonomous symptom, not attributable to paresis, incoordination, or other elementary neurological disorders. It is worth remembering that apraxia was the subject of the first and probably the only group study carried out in the classic era with the aim to ascertain its relation to the hemispheric side of damage. Relying on the side of paresis, Liepmann divided 83 patients with cerebral disease into two hemispheric groups: 41 patients were classified as left-hemisphere damaged, because they had right paresis, and 42 patients as right-hemisphere damaged, because they had left paresis. Apraxia was tested in the healthy upper limb and found in 20 patients of the former group and in none of the latter. It was time to recheck these data on larger samples, submitted to quantitative assessment under rigorous testing conditions. We took care to give test items by imitation and not verbally, to avoid mistaking errors due to comprehension for those due to apraxia. A series of variables were controlled, namely, whether the to-be-imitated movements were meaningful or nonmeaningful, whether they were carried out with the whole limb or with fingers only, and whether they required the imitation of single positions or of motor sequences. None of them was influential. We confirmed the association between IMA and left hemisphere damage: In this group apraxia was more frequent and severe. However, we could also identify a moderate impairment in a few right brain-damaged patients.

Having borne out the left-hemisphere prevalence for gesture production, we addressed the question of the role played by the left parietal and frontal lobe in executing gestures with the left hand (which was the hand left brain-damaged patients used in carrying out the test). Following Liepmann, orders should travel from the left parietal lobe to left prefrontal areas, cross the corpus callosum, reach the right prefrontal lobe, and finally end in the right premotor area. In this view, left hand apraxia is expected to occur with the same frequency and severity in patients with left parietal and left frontal injury. This prediction was not supported in a study in which patients with lesion to either lobe, identified with imaging techniques, were tested on the imitation test: apraxia was found in 75% of parietal patients versus 38% of frontal patients, and in the former group it was remarkably more severe than in the latter. This finding suggests that

left parietal information can be transmitted to the right prefrontal area through other pathways, in addition to that involving the left premotor area, although heterologous transhemispheric connections have not yet been identified.

The interpretative schema proposed by Liepmann conceives of apraxia as a disconnection between the areas of the brain where gestures are programmed and those where they are executed. The pathways connecting them differ depending on the modality used to transmit information and thus it is likely that, in some patients, the lesion is so placed as to produce apraxia when the order is transmitted in one modality and not in another. In a large sample of 150 left brain-damaged patients, Faglioni, Sorgato, and I required the use of the same series of objects on command, by visual presentation, and when they were handed to the blindfolded patient. In agreement with the hypothesis, there were patients who showed wide discrepancies in the scores obtained in the three modalities.

Ideational Apraxia

The defective movement organization underlying IMA must be kept distinct from defective recall of the spatial configuration of the gesture with which an object is used. This kind of impairment was reported at the beginning of the 20th century by Pick under the name of ideational apraxia (IA) and was apparent when patients were requested to show how they would use single objects that they were handed or, better, more than one object. However, the symptom autonomy was accepted with some hesitancy, because most of the patients investigated by Pick were demented or confused. Another knotty issue was the independence of IA from IMA, which, when severe, might so impair movement execution as to make it unrecognizable. The group studies I carried out first with Pieczuro and Vignolo and then with Barbieri showed that IA is even more closely linked to left-brain damage than IMA and cannot be accounted for by intellectual deficit, because patients with IA were not more impaired on the Raven test (a nonverbal intelligence test) than patients without it. Neither could IA be attributed to severe IMA, as there were patients that showed a strong dissociation in both directions, those with very poor scores on IA and normal performance on the IMA test were particularly convincing.

Fifteen years later I revisited IA in a study with Lucchelli, seeking in the qualitative analysis of errors, insights into the nature of the disorder. We were led to stress its independence from other movement disorders and to conceive of it as a specific form of semantic amnesia, characterized by the loss or inaccessibility of the use of object representations and similar, in a way, to the amnesia for other object attributes (their sound or color) reported in a few left brain-damaged patients.

The Birth of *Cortex*

As already mentioned, the only way to expose one's research to the scrutiny of a wider audience and to contribute to the scientific information circuit was to have papers published in journals with an international circulation rather than burying them in Italian journals, which nobody read abroad. The choice may appear obvious today, but it was not that easy 40 years ago, because it implied the acquisition of not only a language but also a style in which to report data, which were unfamiliar to most of us. As a matter of fact publishing in English was then exceptional among Italian neurologists and entailed a high risk of rejection. We concurred that it was a risk worth taking.

More hazardous was the initiative to promote the birth of a journal entirely devoted to the relation of brain to behavior. It started as a local undertaking, but soon gained the support of colleagues from other countries, who shared the idea that it was time to develop a sounding board for the increasing number of people who were interested in neuropsychology. Initially we thought of carrying out the project with the aid of a minor publisher, then we gathered up courage and tried to interest a major one, initially with some success. Then it all went awry, because our man changed his mind and began attributing more importance to being a urban guerrilla than to publishing books or journals (in a few years he would blow himself up on a high-voltage electricity pylon he was trying to fill with dynamite on the periphery of Milan). We had to begin our search for a solution to our problem all over again. In the meantime we learned that Hécaen had taken a similar initiative, which reached its goal a year before ours and was called *Neuropsychologia,* derived from the term used by Lashley to define the new discipline. Finally our project came to fruition and in June 1964 we were able to publish the first issue of the journal, for which we chose the Latin name *Cortex* that, in addition to pointing to the part of the brain most involved in higher mental activity, had the advantage of being readily understood and pronounced in different languages. The editorial board included some of the most prominent neuropsychology scholars, among whom I wish to remember those who in the early days gave the most active contribution to the selection and editing of submitted papers: Arthur L. Benton, George Ettlinger, Norman Geschwind, Harold Goodglass, and Klaus Poeck. The editor in chief was Gastaldi, who also made a financial contribution to enable us to meet early expenses, but the bulk of the editorial work was on Vignolo's and my own shoulders. In 1973, on Gastaldi's death I took over as editor in chief, a position I held until 2000, when Sergio Della Sala succeeded me.

Year after year the circulation and prestige of *Cortex,* as well as the number of submitted papers, increased. It is worth recalling that when Hécaen learned about our initiative, he expressed the understandable

concern that there would be insufficient scientific production to supply both it and *Neuropsychologia.* Yet within a few years the number of journals exclusively devoted to cognitive disorders doubled and then tripled and has now exceeded 10. I found editing a journal an exciting, although exacting job, which requires assiduity, competence, and tact. One of the risks a wise editor should beware of is a blind reliance on referees' opinion, especially when a dispute arises between one of them and the author. The possibility that the referee is wrong should not be discarded, even if he or she is an authoritative scholar and the author young and unknown. This may seem an obvious and trivial warning, but it is easy to forget that at times overly strict adherence to previous personal findings or views can dim the perspicacity of even the most competent referees.

Spatial Disorders

An issue soon addressed by group studies was constructional apraxia (CA), the inability to reproduce a drawing or a block model, respecting its size and the spatial relations among the elements that make it up. The impairment of constructional skills had always enjoyed a certain popularity among neurologists, because of the ease with which it could be demonstrated at the bedside with the mere aid of paper and pencil. Yet its mechanism and relation to the side and locus of lesion had not been clarified. Both Hécaen in Paris and Zangwill in London investigated constructional disorders in hemispheric samples and found that they could follow damage to either side of the brain but were more frequent and severe when associated with a right lesion. Also based on qualitative differences, they drew the inference that CA differed in nature depending on the side of injury: It reflected a defective space perception (spatial agnosia) in right brain-damaged patients and an executive disorder (apraxia) in left brain-damaged patients. We took up this question in several studies and came to the conclusion that hemispheric differences were less neat and replicable than was assumed by other authors, probably due to the fact that too many skills concurred in the constructional performance and made it difficult to disentangle those differently represented in the two hemispheres. My feeling was that constructional tasks would be better abandoned in favor of those that more directly assessed discrete spatial abilities, an area that in the past had been studied only occasionally in few patients showing devastating deficits and that needed a systematic investigation with sensitive procedures. I distinguished four levels in the processing of spatial information and made each of them the subject of a series of studies that spread out in several years: exploration, perception, memory, and conceptualization. I will summarize them in this order, without minding the chronological order.

Head and Eye Forced Deviation

This is a symptom that neurologists are well acquainted with in patients showing the sudden onset of a hemisphere disease (mostly vascular). Their head and eyes are deviated towards one side, which is opposite to the paresis, i.e., they look at the lesion. Although known from the 19th century, the symptom had never been the subject of a systematic investigation. We surveyed its presence and graded its severity in all the patients admitted to the wards for the recent onset of a stroke. Out of 436 patients, gaze paresis was found in 120 and showed a striking hemispheric asymmetry, being more frequent, severe, and long-lasting in those with right brain damage. Also the underlying lesional pattern differed: It corresponded preponderantly to post-Rolandic damage when the injury was on the right side and to the involvement of the entire territory of distribution of the Sylvian artery when it was on the left side. This suggests that oculomotor centers have an asymmetrical organization in the two hemispheres, focalized on the right and diffuse on the left.

Neglect

A less blatant manifestation of defective space exploration is the tendency to disregard stimuli occurring in the space contralateral to the lesion, which is observed in some right brain-damaged patients, in spite of their preserved ability to move their head and eyes in any direction. It is amazing how little attention this symptom drew before the 1940s, even though its effects on a patient's behavior are so remarkable that we now consider it second only to aphasia in terms of clinical and rehabilitative impact.

In our investigation of neglect, we started from Kinsbourne's hypothesis that neglect results from the disruption of the balance between the mechanisms controlling in each hemisphere the shift of attention to contralateral space. According to this view the emphasis is not on the lack of attention to the left space but on its focus on the rightmost space. To test this hypothesis we projected a four-letter horizontal string in the patient's right field and measured the time it took the patient to decide whether a target letter, whose position varied from trial to trial, was capital or small. In controls and right brain-damaged patients without neglect, reaction time was unaffected by the target position, whereas in patients with neglect it was shortest for the rightmost letter and progressively increased as the target was displaced to the center of the screen. This apparent paradox—longer reaction time for stimuli closer to the fixation point—provides evidence that in neglect patients, the rightmost stimulus exerts a sort of magnetic attraction, which traps their attention in the space ipsilateral to their lesion.

If neglect reflects a disorder of attention, it is supposed to affect other modalities, in addition to the visual one, in which it is almost exclusively

investigated. First, we tested the tactile modality, by asking blindfolded patients to explore a symmetrical maze engraved in a board with the hand ipsilateral to the lesion. The exploring hand started from the central position of the maze and then traveled through its alleys in search of a marble, which was put in one of the four ends (upper and lower left and upper and lower right). In both hemisphere-damaged groups, the search time was longer when the marble was in the space opposite to the lesion, attesting that exploration was steered by the contralateral hemisphere. However, failure to find the marble in 90 second was only present in patients with right-sided injury and visual field defects, the same brain-damaged subgroup usually impaired in the visual modality. Analogous findings were obtained in a similar test, in which blindfolded patients were seated in front of a computer keyboard and informed that 10 keys, symmetrically arranged to the left and right of the midline, emitted a sound when pressed. Their task was to find the sounding keys, pressing whatever key they wanted in 10 successive trials. Right brain-damaged patients with visual neglect showed a clear-cut tendency to avoid entering the left space. The question raised by this and the previously discussed experiment is what kind of information guides the movements of the exploring hand in space. It springs neither from vision, as the patient was blindfolded, nor from tactile perception, as the stimuli processed by the finger only concerned the point where it was and contained no spatial information. Searching movements have to be steered by the maze or keyboard mental representation the patient is building on the basis of the kinesthetic input, possibly transformed in visual images. Accordingly we conceived of the patients' tendency to neglect the contralateral space as secondary to a "dimidiated" space representation. This was the first hint at the existence of a representational neglect, the role of which was to become the focus of Bisiach's astute clinical remarks and ingenious experiments.

Hints that neglect can also play a role in the auditory modality are suggested by the behavior of patients who answer questions from an examiner placed at their left by addressing a second examiner placed at their right, even if their voices are supposed to sound quite differently, being the voice of a man and a woman, respectively. We also developed a purely acoustic test, in which the patient was requested to detect the interruptions occurring in a continuous sound delivered to either ear through earphones. In the monaural condition, the sound was sent to one side only and, consequently, patients knew in advance the ear on which they had to focus; in the binaural condition, the sound was received by both ears and could be interrupted in either of them, obliging patients to keep both under surveillance. The task was easy to perform for control or left brain-damaged patients, none of whom failed to detect any interruption, but turned out to cause left-ear omissions in one third of right brain-damaged patients, especially in the binaural condition. Their lesion was located in the parietal lobe or the

thalamus, areas that are also implicated in visual neglect. Yet visual and auditory neglect cannot be viewed as an expression of the same phenomenon in two sensory domains, as there are patients who show the former but not the latter and vice versa.

Disorders of Space Perception

It is extremely rare to encounter patients with unilateral brain damage who are impaired in judging object space orientation in everyday life or who fail to recognize an object, because of its inclination. However, if space perception is assessed with graded, quantitative measures, a deficit emerges clearly, provided we use elementary tasks, which minimally involve other cognitive skills. The test we found most sensitive required only reproduction of the orientation in space of a segment. A model was presented, made up of a pair of rods, connected vertically at one end by a hinged joint, with the lower rod mobile on the horizontal plane and the upper on the vertical plane. This made it possible to orient the upper rod in any position in space. The patient was also given another pair of rods and requested to manipulate them in such a way as to put the upper rod in the same position as that of the model. In one condition, the task was carried out with the aid of vision, in the other with the patient blindfolded. In both conditions, a defective performance was found only in right brain-damaged patients with visual field defects; all other brain-damaged groups were indistinguishable from normal controls. It is worth mentioning that at a time when the intrahemispheric locus of lesion could not be determined, we used the presence of visual field defects (VFDs) as a marker for damage extending posterior to the Rolandic fissure. If right and left brain-damaged patients with VFD performed poorly on a visual test, it was impossible to state whether the impairment was due to defective vision or to injury to posterior areas; if, however, only one of the hemispheric groups with VFDs had poor scores or both were impaired, but the task did not involve vision (e.g., it was a tactile task), then we interpreted the results as pointing to the specialization of posterior areas for the skills we were testing.

In another study, unilaterally brain-damaged patients were given a more complex tactile perception test, in which they had to run the extended forefinger of the hand ipsilateral to the lesion along the raised outline of a meaningless block, without viewing it, and were then requested to identify visually its shape on a multiple-choice display. Presumably this task is more difficult than the rod test, as block recognition is dependent on the ability to integrate in one spatial pattern the successive changes of orientation made by the moving finger. In support of this hypothesis we found that all hemispheric groups, with or without visual field defects, performed more poorly than normal controls. Also the hemispheric side of lesion was an influential factor, right brain-damaged patients being more impaired

than left brain-damaged patients, whereas the posterior location of lesion did not cause an additional impairment, as was the case for the rod test. In another study, we contrasted the performance of unilaterally damaged patients on intelligence tests involving spatial skills, such as the Raven test and the Block Design and Picture Arrangement subtests of the Wechsler, and found no difference associated with the side and site of lesion, the only significant variable being the presence of brain damage. Intelligence tests had been the first to be used to detect hemispheric differences in spatial performance, but they yielded inconsistent results, probably because the many abilities they involve make them sensitive to lesions in different areas.

Spatial Memory

We studied the relation of this form of memory to hemispheric damage with the tests devised by Brenda Milner and her coworkers, Corsi's test and a maze learning test. The former presents the subject with cubes glued to a board, which are tapped by the examiner in a pseudo-random sequence of increasing length. The patient is requested to reproduce the tapping pattern either immediately after the examiner (short-term memory) or after a filled delay (long-term memory). Our studies confirmed that these two forms of spatial memory are separately organized in the brain, in agreement with what is know for verbal memory: Not only can a double dissociation be found in their performance but they are differently associated with the lesion site and side. Although no hemispheric effect emerged with short-term memory, a definite impairment of right posterior patients was brought out by the long-term memory procedure. The sensitivity of the maze learning test to long-term memory deficit found support in the performance of a patient who suffered from topographical amnesia, the inability to find one's bearing in unfamiliar or, in the most severe cases, even familiar surroundings. In spite of the fact that our patient's difficulty was limited to learning new pathways, she was still unable to master a simple version of the maze, after 250 trials, given in blocks of 25 trials a day for 10 days

Balint's Syndrome

An impressive syndrome, which represents an epitome of spatial disorders, is that reported by the Hungarian neurologist Balint in 1909 following bilateral damage to the parietal lobes. It consists of gaze apraxia, misreaching, and extreme narrowing of visual attention. In a patient of this kind whom I had the opportunity to observe, the spatial disruption was not limited to vision, as is the rule, but extended across all modalities. He was not only completely unable to direct his gaze and to reach out for an object presented in any part of his visual field but also failed when the

stimulus location depended on tactile or acoustic information, e.g., when he was requested to direct his gaze or to grasp with his hand the thumb of the other hand or a ringing bell.

Career Moves

In 1959 I gained *libera docenza* and became Gastaldi's *"aiuto"*. In 1967, the Italian Society of Neurology chose hemispheric dominance as a topic for one of the main sessions of its Congress and I was invited to give a talk. In the world of academia, the role of speaker at the national congress was much longed for, as it gave the selected person the chance to be in the limelight and to show the quality of his or her research. My lecture focused on the findings my colleagues and I had been collecting during 6 years of research on a wide range of neuropsychological topics and was supported by slide projection, an uncommon practice at that time, which allowed me to speak and not read a long and tedious text. Nowadays it may be difficult to imagine how boring a conference could be in those days when lectures were not pepped up by data presentation and when the long and sometimes involved sentences of the text were read hastily, for fear of running out of time. Initially I too made these kinds of mistakes, but soon learned that, no matter how many rehearsals you need, your speech should never be read. The approval of the audience was due not only to the wealth of data I had to offer but also to the flavor of novelty of the statistical approach employed, even though a few old clinicians turned up their noses at the suggestion that only differences associated with a given probability be accepted.

Meanwhile neuropsychology was becoming a popular topic in a number of neurological departments, where young students gathered around Guido Gainotti, Gianfranco Denes, Dario Grossi, and other researchers whose names were beginning to spring up in the international literature. Other centers blossomed in neurophysiological departments and in the psychological departments that were developing in a number of universities, with Carlo Umiltà, Luigi Pizzamiglio, and Carlo A. Marzi as leading figures.

My time was largely taken up by research, but I was not deaf to forewarnings from the society. By the late 1960s, students all over the world were staging protests against the manifold manifestations of power abuse in international and national relationships. Vietnam and the nightmare of the atomic war were sensitive issues, which stirred up the hearts of millions of people and gave rise to public demonstrations and rallies. From time to time I joined them. More domestic themes were the fight against old privileges and social injustice and the incongruity between the economic growth after the war, which had brought Italy closer to the model of the most advanced European countries and the delay with which a few obsolete institutions were reformed. Among these were our universities.

There were insufficient facilities to cope with the growing number of students coming from all social layers and the teaching methods had to be thought over again, in view of changed requests. Especially in big cities, like Milan, university life was upset by students protests, which I supported at least in part. In particular I thought that a few good steps could be taken toward a reform of medical studies and that we, young researchers, had to stand by students and add credence to their demands. For instance, we could show our solidarity by proposing a new methodology of teaching, with students divided into small groups and assigned to a tutor, who reduced formal lectures to a minimum, emphasized bedside teaching, and at the end assessed the students' preparation first directly on the patient and then with a questionnaire. This model was tried for a few months, with the approval of Gastaldi, who contributed to putting it into effect. However, this was not the opinion of most of his colleagues, who were horrified at the prospect of seeing their subordinates performing the duties that qualified their own role at the top of the career ladder and spoke of a *coup d'état.* Actually what they considered little less than a preliminary to the assault and seizure of the Winter Palace in St. Petersburg, 1917, was the teaching system adopted by several American schools of medicine. I also took part in the activity of a group of young lecturers, who strongly believed in the need of a reformation in medical studies and sought to settle its principles and to outline the guidelines for a reform bill. Our efforts resulted in a booklet, which we tried to distribute among people working for the university and Members of the Parliament, hoping that it would receive some attention. Just one of the latter acknowledged its receipt. Unfortunately I did not keep a copy of the booklet and so I am not in a position to say what I would think of it today. I strongly suspect that we were guilty of levity and overconfidence, as always happens when a problem is solved by looking at a theoretical model, without considering the social forces at work. Even if this episode was a little farcical, it does bear witness to an atmosphere of hope and commitment that was typical of 1968 and represented a high point in democratic participation. I must add that neither students nor full professors showed any appreciation for our initiative. The former seemed more interested in a palingenetic process of rebirth and did not care about practical trivialities, the latter considered it as an inadmissible and offensive attack on their powers of authority. A few years later I was to learn that their resentment was still very much alive.

In 1969 I was called to hold the Chair of Nervous and Mental Diseases by the School of Medicine, which had been recently set up in the University of Trieste. My position was that of Professor on an annual contract and not yet that of Full Professor. However, the fact that it entitled me to hold the ward direction stood me in good stead in the next Chair competition, which in fact I won in 1971. Surrounded by Carso stony hills and reflected

in the crystal clear water of the Adriatic sea, Trieste was a charming city, molded on a middle European rather than an Italian model and rich in traditions inherited from the time it had been at its most prosperous as the Hapsburg empire's main harbor. Its recent history had been marked by ethnic conflicts, which had left bloody wounds destined to only heal with the passage of time and generations, as in fact it did. My family and I liked the city and I would have been delighted to stay on for good, had the working conditions been adequate. Unfortunately they were not: The hospital was an overcrowded building of the 19th century, research facilities were practically nonexistent, and the staff was inadequate. Fearing to have little chance of overcoming these drawbacks and of creating a vital research center in Trieste, I decided to go back to Milan, even if this choice implied at least for a time a step back in my career, because it meant renouncing Full Professorship. With the benefit of hindsight one might say that what the future held for Trieste was the flourishing of several scientific centers and in particular of a branch devoted to cognitive neuropsychology, which was to be guided by Tim Shallice. This development occurred, however, several years later and I was reluctant to waste time, in the absence of clear indications. Back in Milan, I collaborated with Gastaldi in teaching neurology and got involved in research again with the members of our group.

As our research grew and its results were published and known, the opportunity to get into touch and establish personal relations with foreign colleagues increased. At first this demand was met by the initiative taken by Hécaen since the early 1950s to invite neurologists from different countries to convene in one of the beautiful resort places or art sites, which make Europe so attractive, to discuss subjects of common interest in an informal and relaxed atmosphere. As the years went by, the meetings were opened to a larger number of continental and overseas participants and their schedule became more rigid, but they maintained a well-balanced distribution of time for talking and time for discussion. It is no wonder, therefore, that several people agreed to reserve one of their holiday weeks (precisely the last week of June) to attend the International Neuropsychology Symposium, as it came to be known. Their format was certainly suited for developing more intimate relationships among scientists and for favoring their exchange of information. In the 1960s a more formal society was created, the European Brain and Behaviour Society, with the aim to bring together scientists from different sources who were interested in the biological underpinnings of behavior. I participated in the preliminary discussions to create the Society and had the honor to be nominated as its president for the biennium 1971–1973. Approximately at the same time, a comparable initiative was taken in Italy, where a branch of the Italian Neurological Society was devoted to the study of cognitive disorders and was open not only to neurologists but to anyone qualified in

research and wishing to participate. Formal requirements were kept to a minimum and from then on meetings have been held twice a year and from time to time have been organized in conjunction with other national societies.

Disorders of Object Recognition

A theme that repeatedly attracted my attention and was the subject of group studies as well as of single case analyses was agnosia, which represents along with aphasia and apraxia one of the three broad areas of cognitive impairment identified by neurologists before the First World War. It designates disorders of recognition and is classified according to the stimulus type (object, face, color, sound agnosia) and the sensory channel through which information is transmitted (visual, tactile, or auditory agnosia). Lissauer, a 26-year-old student of Wernicke, who reported the first clearly documented case of visual agnosia, stated that there are two main forms of the deficit, depending on the stage at which the visual information processing breaks down: apperceptive agnosia when the patient fails to achieve the three-dimensional structural representation of a stimulus and associative agnosia (such as that of the patient he described) when the stimulus is perceived correctly but is not associated with its meaning. Few cases of either type had been published since and for some of them the interpretation remained contentious (see Goldstein and Gelb's patient Schnee, who was suspected of being a malingerer), so that the very existence of agnosia was questioned.

To overcome the stalemate produced by the apparent rarity of agnosic patients, Faglioni, Spinnler, and I devised the strategy to tackle recognition disorders by investigating the contribution made by the two hemispheres to the processing of visual information. To this end we gave patients, with unilateral brain lesions, visual tasks that were either demanding in terms of perceptual discrimination or were calling for a semantic association, e.g., matching similar meaningless stimuli vs. matching objects of different shape but with similar functional meaning (a traditional key with a Yale key). Right brain-injured patients failed the perceptual tests and left brain-injured patients the associative tests, in keeping with the findings of other experiments, in which non-object stimuli or even nonvisual stimuli were used to assess perceptual and associative skills. For instance, right-sided patients were impaired in hue discrimination (Farnsworth's test) or in judging whether pairs of meaningless sounds presented in succession were the same or different, and left-sided patients were impaired in selecting the color typical of an object (red for cherries) or in matching a meaningful sound with the corresponding picture (mewing with cat). By and large these data are compatible with the hypothesis that the right hemisphere plays a

dominant role in perception and the left hemisphere in semantics, a specialization that, when disrupted, gives rise to apperceptive and associative agnosia.

The theme of agnosia returned in studies undertaken a few years later, which benefited from the introduction of imaging techniques that were able to localize *in vivo* the lesions of the great majority of patients. Thus, we could gather patients with computed tomography (CT) scan evidence of left posterior cerebral artery (PCA) infarct, which is held responsible for a typical visual-verbal disconnection syndrome, due to the interruption of the fibers linking the undamaged visual area (right occipital lobe) with the undamaged language center (Wernicke area in the left temporal lobe). As a result, patients suffer from alexia and color anomia, being unable to associate graphic signs with their linguistic value and colors with their names. In contrast with this deficit, patients are claimed to show a preserved ability to name visually presented objects, a discrepancy that represents a challenge for the disconnection hypothesis. Geschwind speculated that object visual images avoided the block by activating tactile images in the ipsilateral parietal lobe, whence they would reach the left language center via the fibers crossing the corpus callosum, anterior to the lesion. A further reason of perplexity is that a left PCA infarct had also been found in the patients reported by Freund (1899) and Lissauer (1900), the former complaining of an object naming inability limited to the visual modality (optic aphasia) and the latter of object associative agnosia. Thus, what are the consequences of a left PCA infarct? Alexia with color anomia, optic aphasia, or associative agnosia? There was clearly a need to marshal new data. We collected 16 cases with CT scan evidence of left PCA infarct and tested their reading and color naming ability along with that of naming objects presented visually, tactually, and through a verbal definition. The claimed divergence between letters and colors vs. objects did not exist. The majority of these patients was alexic, color anomic, and object anomic, of comparable severity in both the visual and tactile modality. These findings deserve a few comments. First, the failure to associate visual stimuli with their verbal code, far from representing an exception, is the rule following left medial occipital lobe damage. Second, naming objects does not differ substantially from color and letter naming and, therefore, does not require an *ad hoc* interpretation. Third, the boundaries between visual agnosia and optic aphasia require further investigation. As mentioned previously, optic aphasia is assumed to affect visual naming but not recognition. The evidence provided by Freund in support of this statement were the patients' claim to have recognized the object they failed to name or the circumlocutions they used, which contained clues pointing to a successful identification. Nowadays, one is supposed to assess stimulus recognition with stricter criteria, using nonverbal tasks calling for category grouping, semantic matching, miming object utilization, etc. However, even one patient who qualified

for the diagnosis of optic aphasia, having passed these tests, was found to be problematic by Alphonso Caramazza, in that he revealed an inadequate knowledge of the object's semantic properties. The same occurred in a patient I investigated with Saetti. His semantic recognition was correct according to all of the criteria set out for the diagnosis of optic aphasia, but turned out to be flawed when task difficulty was further increased, e.g., when in a matching to sample task all of the stimuli bore a semantic relation to the target and he had to choose the one that showed the strongest association (select the object most closely connected with a thimble among scissors, a threaded needle, a button, reels of thread). Also on miming, his performance depended on the nature of the task: He passed when the gesture was evoked verbally, but failed when it was evoked visually or when the examiner himself carried out the miming and he had to point to the corresponding object. These findings prompt two conjectures on the nature of visual recognition disorders. First, associative visual agnosia and optic aphasia are not two discrete symptoms, but lie on a continuum of impairment and share a common mechanism, characterized by a defective and a compensatory component. The former is the failure of visual information to gain access to the left hemisphere, due to the lesion interrupting of information transfer from the right occipital cortex to the left temporal lobe. As a result, the patient not only is deprived of the ability to attribute to the perceived stimulus its name (optic aphasia) but cannot or can only imperfectly avail himself of the wealth of semantic knowledge stored in the left hemisphere (agnosia). The compensation factor is conditioned by the extent to which the recognition deficit can be made up by the semantic potential of the right hemisphere, which varies across subjects but does not usually match that of the left hemisphere. This hypothesis is in agreement with the dominant role of the left hemisphere in semantic processes, demonstrated by our group studies. Thus, optic aphasia and visual agnosia share the same lesion and the disruption of the same mechanism and differ depending on the right-hemisphere semantic capability the patient had acquired premorbidly.

Tactile agnosia was the subject of the last research I carried out before retiring. Disorders of recognition have rarely been reported in the tactile modality, because they usually affect one side of the body (contralateral to lesion) and, therefore, their detection is obscured by the concomitant presence of sensory deficits. The patient I studied with Saetti had suffered from repeated occipital infarcts, which had caused cortical blindness and tactile agnosia. The parietal primary and secondary somatosensory cortices were undamaged and the patient showed no deficit of either elementary sensations or the ability to perceive the so-called intermediate tactile qualities (texture, weight, size, and length discrimination). We had, therefore, to assume that the severe impairment of object and letter recognition we found in both hands was attributable to a deficit not related to tactile

information processing. We held that its source was the striking failure in tactile spatial performances the patient showed at both the perceptual and imaginative level. He made a lot of errors in judging line spatial orientation and, when given the rod orientation test, described earlier, he was unable even to conceive of how the task could be carried out, a failure I had never found in patients with damage limited to the right hemisphere. The imaging impairment was highlighted by his inability to estimate the spatial relation between two elements of a conjured up object (Is an ox's tail above or below its horns?). We posited that in the tactile modality, severe spatial disorientation could result in a recognition deficit, while the same does not occur in the visual modality, as suggested by the absence of object agnosia in patients with Balint's syndrome, i.e., the utmost form of spatial disorientation. We speculated that, in visual perception, a global apprehension mode prevails, which permits one to analyze the stimulus shape straight-away, while when information is gathered through palpation, stimulus recognition is critically dependent on the ability to make a piecemeal reconstruction of how adjacent parts are oriented and related spatially.

Modena

In 1973 Gastaldi died. As his "*aiuto,*" I was supposed, according to academic rules, to receive from the faculty the temporary appointment to direct the department, until a new director could be selected. The fact that I was totally ignored, in spite of having been qualified as a Full Professor in a national competition, came as a warning to me that the faculty had not forgotten my commitment to the 1968 movement and did not welcome my staying on in Milan. Thus, when the faculty of Modena offered me the Chair of Nervous and Mental Diseases the following year, I was pleased to accept.

Clinical duties were exacting in Modena, as I was the chief of a department with 70 neurological beds and 40 psychiatric beds. The first thing I did was to entrust the psychiatric beds to a colleague who taught psychiatry without having patients and to devote all my time to neurology. There were a few unfilled positions in the team, which I offered to young doctors who were specializing in Milan or Modena. Thus, I could rely on the cooperation of enthusiastic colleagues, eager to learn, carry out research, and assist me in teaching students. Their clinical experience was necessarily limited and, at least in the earlier years, called for my continuous supervision and advice at the bedside, but eventually they became skilled clinicians and experts in their own area of specialization. That gave me the opportunity to learn a lot from the discussions about patients I had with them during the rounds.

Throughout my career I have enjoyed the variety of activities and duties, associated with the role of clinical professor, which are somewhat different from those accomplished by other neuroscientists. Looking through the list of the contributors to the previous volumes of this series it would seem that I am the first to represent this category—clinicians; it might, therefore, be appropriate to discuss the extent to which patients' treatment, research, and teaching interact and interfere.In the present context, I assume that clinical activity is limited to that carried out as a consultant in the wards and outpatients' clinic and does not involve private practice, because profit has its own psychological dynamic, which tends to dominate over other engagements. By and large, my feeling is that the medical profession is more akin to that of a judge than of a lawyer, in that the needs it is supposed to meet are entitled to receive an answer proportionate to their nature and not to the subject's status. This right is not guaranteed if the client must pay the doctor's honorarium.

The issue of the extent to which clinical duties are compatible with those entailed by research and teaching can be addressed from a subjective or an objective standpoint, namely, in terms of personal satisfaction or of proficiency. Subjective evaluations are obviously dependent on personality and circumstances, and I can only cite my own experience. I always felt that the opportunity to shift from patient examinations to research and teaching, far from causing loss of concentration and dissipation of energy, is an asset, because it keeps your mind open and inquisitive on a wide range of practical and theoretical aspects of reality and can be immensely gratifying. In the latter respect, the medical profession is unique. Perhaps people are less familiar with its intellectual appeal and do not realize how much it has in common with the work of detectives, as they sift their way through heaps of irrelevant information in the search for the small clues that allow the formulation of hypotheses on the culprit. Doctors have to display similar skills in their endeavor to pick out the thread that leads to the correct diagnosis, identifying it from among the often hazy and sometimes downright misleading descriptions patients provide of their ailments. Learning to bridge the gap between theory and practice is a requisite for all professional activities, but in none is the distance so wide as in medicine. Books and formal lectures teach students a rational tale, where and what the illness causes, the somatic changes it produces, and the deriving signs and symptoms reported according to a logical and self-explanatory plan. Doctors, however, are faced with a different task: They must learn to discard accounts that miss the point, to raise questions that often are not obvious and to combine apparently unrelated bits of information, namely, an array of procedures that are only mastered when experience is coupled with shrewdness and knowledge. This is a combination that remains crucial even in times, like ours, when technology is claimed to be able to solve any problem, a dangerous

belief that we, as teachers, are supposed to discourage, if young doctors are to resist the temptation to rely on machines instead of their own brains.

The other side of the coin is whether having to attend to three different activities helps or hinders your performance of each. There is agreement that at least in principle teaching improves both clinical and research activity, as nothing helps more in clarifying one's own thought than having to explain it to other people. That is not to say that being a clever doctor or researcher guarantees success as a teacher, because neither logic nor insight are a safeguard against the risk of being boring when speaking on a well-known topic. A more delicate question is the competition for time between clinical practice and research, a subject of a recurring polemic against clinicians heavily engaged in research, who are sometimes accused of having a narrow circle of acquaintances and of being more familiar with test tubes and centrifuges than real patients. The point at issue is the extent to which the expertise acquired in one's own field of research is transferable to daily bedside activities and can enhance diagnostic skills across a wide range of diseases. I hope I will not be accused of being biased, if I claim that neuropsychology is an area of great synergy between research and clinical neurology. First of all, at least some of the cognitive disorders we study are frequently encountered, being present in a large gamut of diseases of different etiologies, practically all of those encroaching on the hemispheres, and have a definite localizing value. The ability acquired in detecting and testing them gives the neurologist a wider perspective on an array of signs and symptoms, which, if not properly investigated, may escape the standard examination and give the false impression of its negativity. Alternatively, they can be mistaken for the manifestation of a psychiatric disorder and lead to wrong measures, as it happens when the jargonaphasia patient's speech is attributed to mental confusion or hysteria and treated accordingly. I remember feeling great professional satisfaction when I was able to reverse an ophthalmologist's diagnosis of hysteria in a patient, whose inability to recognize familiar faces dated back to more than 3 years. The diagnosis had been accepted by the general practitioner and shared by his relatives, but not by the patient himself, who was delighted when I told him that the name of his disability was not hysteria, but a long Greek name that seemed a tongue twister, prosopagnosia. Yet it must be recognized that the ophthalmologist's sin was venial, because in the 1960s this strange deficit was unknown even to most of neurologists.

Prosopagnosia

The inability to recognize familiar faces, or prosopagnosia, represents a special case of agnosic deficit, which does not extend usually to other stimulus categories and is often associated with a lesion confined to right hemisphere

areas, which is not found in other forms of agnosia. These are notions acquired following a debate that dragged on for several years and was also made harder to settle because of the rare occurrence of these patients. For instance, in the course of a 50-year experience with neuropsychological patients, I could count the number of prosopagnostics I saw personally on the fingers of my hand.

Faced with this drawback, Spinnler and I devised to circumvent it by giving face recognition tests of graded difficulty to hemisphere-damaged patients. This procedure allowed us to study milder and clinically silent forms of the deficit and at the same time to test the hypothesis of its association with right brain damage, which Hécaen had suggested on the basis of the few cases with autopsy available in the literature. Because familiar face knowledge differs from person to person, we used unfamiliar face snapshots and administered them in matching and short-term memory tasks. The data from this and subsequent studies pointed out that right brain-damaged patients, especially those with posterior injury, performed poorer than left brain-damaged patients and extended, therefore, the generality of Hécaen's hypothesis to unfamiliar faces. The hemispheric asymmetry found with them was analogous to what we had discovered with other types of visual stimuli (meaningless figures, colors, etc.) when the patients' perceptual abilities were tested with exacting tasks and suggested that prosopagnosia may be just an aspect of a more general deficit in discriminating subtle perceptual differences (remember how similar are human faces). However, it is unclear whether this account also holds for familiar face recognition, which represents the gist of prosopagnosia and can be due either to a perceptual deficit or the disruption of the known face semantic store or both mechanisms. This is a question that can only be answered by examining prosopagnostic patients, as we did with three of them 20 years later. The method devised with Faglioni was to give to 100 normal subjects unfamiliar and familiar face recognition tests, assumed to assess perceptual and semantic memory abilities, respectively. On the distribution of the difference between the unfamiliar and familiar test scores, we computed the thresholds that corresponded to the internal and external tolerance limits and allowed the identification of subjects who were outliers for an exceedingly poor performance on perceptual or semantic memory tests. Thus, we had a measure that permitted us to classify prosopagnostics as predominantly apperceptive, predominantly associative-semantic, or failing in both dimensions. When we gave the battery to our three patients, we found that they were distributed among the three categories, one failing predominantly on familiar faces, one on unfamiliar faces, and one being equally impaired on both. It would appear, therefore, that the relation of prosopagnosia to the right hemisphere reflects the preeminent role of this side both in processing perceptual information and in storing human face representations.

Is the poorer performance of right brain-damaged patients in face tests, combined with the outcome of Hécaen's review, to be taken as evidence that prosopagnosia depends critically on injury to the right side of the brain? Or does a clear-cut deficit in recognizing familiar faces always have to be associated with bilateral damage? In favor of the latter hypothesis, one can cite the extreme rarity of the disorder: Although dyslexia follows with a certain regularity left PCA infarcts, most right PCA infarcts are not associated with prosopagnosia. Even more supportive of bilateral damage was an early review of the autopsied cases of prosopagnosia, made by Damasio, who inferred that lesion to both hemispheres was a feature of all of them. Their small number, however, cautioned against drawing definite conclusions. Twelve years later, I addressed the issue relying on the much larger number of cases submitted to imaging techniques (CT and MRI), which are accessible nowadays. With respect to autopsy findings, they enjoy the great advantage of being available in practically every patient who complains of the disorder and not only in those who die (obviously a subsample biased for its severity) and of coinciding with the time of the clinical examination and not with the end of disease (during which new damage may have occurred). The survey of the literature yielded the retrieval of more than 30 cases of prosopagnosia with lesion confined to the right hemisphere (confirmed by autopsy in two patients) and thus produced conclusive evidence that a right-sided injury is sufficient to produce prosopagnosia.

In carrying out this research I had the generous help of Dr. M. Kawamura, who kept me abreast with the cases published in Japanese journals, a source of information unavoidably ignored by the western literature. I had met him during a scientific trip made in Japan at the invitation of the local neurological society to lecture on prosopagnosia at its Congress. Thanks to his warm hospitality, my stay in Tokyo was pleasant and relaxing and I was delighted to discover that he was a bibliophile, an enviable owner of a collection of 19th century neuropsychology books that he had managed to find in antique bookshops. Incidentally, if one is curious about what happens in the world, visiting foreign countries and getting to know colleagues in their own environment is one of the most attractive aspects of our work, as it gives us an intimate knowledge of the heart of a country. There are many facets of the way of life and thinking of foreign people and of the social issues they face that one comes to know better and to appreciate while chatting over a good bottle of wine, whiskey, or (as in the case of Kawamura) sake. Conversely, it has always amazed me to meet colleagues of high scientific standard and intelligence who show very little interest and ask few or no questions about countries they visit for the first time, as if events, habits, and feelings of foreign people were somehow beyond their mental horizons.

A central and recurring issue of prosopagnosia is its specificity, namely, whether it reflects the disruption of an anatomo-functional apparatus

devoted to faces or is but an aspect of a more general visual recognition impairment, which extends to other stimulus categories, provided either of the following conditions occurs: (1) The category exemplars share the same degree of figural similarity as faces do and thus can be compared to them in terms of perceptual difficulty. This argument is supported by the finding that there are patients, whose errors involve, in addition to faces, other categories, such as car makes or some kinds of animals, which have the previously mentioned features. Particularly impressive was the case report of an ornithologist, who lost the ability to discriminate birds of different species and to discriminate faces. A possible account of these cases is that they suffer from a minor form of apperceptive agnosia, affecting any perceptually demanding task and apparently preeminent with faces, because these stimuli are so relevant socially. (2) Object and face recognition is tested with the same kind of tasks. Lhermitte was the first to point out that we raise different questions to assess object and face recognition. When presented with objects, patients are supposed to say the name of the category to which they belong (it is a hammer); when presented with faces, the name of the exemplar (he is Bob Dylan). The assumption is that, were objects assessed with the same test used for faces, they too would be found impaired in these patients. The remark is pertinent; whether it also is valid is worth testing. In order to verify it, I requested two associative prosopagnostic patients to identify their personal belongings (e.g., their own wallet, glasses, electric razor, etc.) from among objects of the same category and their own handwriting from among other handwritings. Neither patient showed the slightest uncertainty in choosing his own belongings. Thus, there is evidence that, at least in prosopagnostic patients with an associative defect, the deficit is specific for faces.

At the end of the 1970s a model of investigating cognitive disorders was introduced, which placed new emphasis on single case study but adopted a new conceptual framework for their interpretation. Unlike the traditional approach, the focus was no longer on anatomic-clinical correlations, but on the identification of the module that was damaged, in the chain of those involved in processing incoming information. The module sequence and its disruption is reconstructed by comparing patients sharing a broad functional disability (e.g., dyslexia) but who perform differently according to the nature of the task (e.g., reading meaningless or meaningful words). These studies represented the extension to brain disorders of the principles of cognitive psychology, but they also took advantage of the progress made by behavioral psychology in improving test construction and their quantitative assessment. They provided a wealth of information on the architecture of the mind and opened new paths to disentangling the cognitive disorder's fine-grained structure, although the cogency of the inferences they draw is somewhat weakened by the absence of any reference to the biological level.

After all, differences in function must correspond to different patterns of lesion.

I was impressed by cognitive models and appreciated their power to improve our skill to discriminate disorders and to disclose dissociations that, amazingly, had been completely neglected in the past. However, they should be viewed as complementary and not alternative to group studies, which retain their heuristic potential in tackling issues relevant to clinicians and, when addressed to the right questions, provide definite answers. An example are frontal signs.

Frontal Signs

The frontal lobe has paradoxical features that have long puzzled neuroscientists: In humans, the size of its anterior areas has increased more than that of any other brain region and there is consistent evidence that they play a role of paramount importance in controlling behavior; yet their damage does not result in signs or symptoms that stand out enough to capture the observer's attention. It is true that some of these patients show amazingly queer behaviors, but they almost always ensue bilateral damage, whereas unilateral injury is associated with subtler deficits, interesting theoretically, but of questionable diagnostic value in the single case. In view of these limitations, we set out with the idea of focusing on a few stereotyped and forced behaviors, easy to elicit at the bedside, which had been occasionally pointed out following unilateral frontal injury, but whose frequency, specificity, and localizing value had not been established definitely.

The first symptom to be investigated was grasping, the reflex closure of the patient's hand on the examiner's fingers when they exert a pressure on his or her palm. It is physiological in the early months of life, but then is progressively inhibited by frontal neuronal networks, whose damage is claimed to cause its reappearance. We tested grasping in 151 patients with disease not involving the brain, who were all negative and 340 patients with hemispheric damage, 26 of whom were positive. In most of the latter, the lesion was localized by CT scan in the medial frontal lobe. Among patients with damage to this area, 70% were positive, an amazingly high percentage, whose weight for diagnostic purposes is enhanced by the absence of grasping in patients with retro-Rolandic damage.

Two other peculiar behaviors, pointing to frontal lesion, were highlighted by Lhermitte: imitation and utilization behavior. In the former, patients repeat compulsorily whatever gesture or vocal expression (words or other sounds) the examiner makes when he is looking at them from a frontal position. In the latter, they use objects, which happen to be on the table within their reach, independently of any request or need. I studied both, following a fixed procedure, in a sample made up of 52 patients with

frontal lesions and 26 with damage to other hemispheric areas. Imitation was observed in 39% of frontal patients and in none of the nonfrontal ones. When present, it was always a massive phenomenon, consistent through repeated sessions, which the patient could inhibit if strongly requested by the examiner but that reappeared inexorably after a short interval, the embarrassed justification being "I thought you wanted me to imitate." Differently from Lhermitte, I found it following lateral and medial, but not orbital, frontal lesions. Compared with imitation, utilization is a much rarer (present in two frontal patients only) but very impressive phenomenon: It is astounding to see a patient so intensively absorbed in the use of objects, simply because they are present and beyond any request and purpose.

Amnesia

Memory disorders are probably the cognitive symptom most often complained of by patients and observed by doctors, even though usually they are but the earliest and most striking aspect of general mental deterioration. More rarely they occur in isolation, linked to damage to specific limbic and diencephalic structures and characterized by the predominance of anterograde over retrograde amnesia and by sparing of semantic and procedural memory. Following Milner's seminal papers, the symptomatic pattern of so called global amnesia is well known, but from time to time patients are reported who differ from the classic syndrome in terms of etiology, evolution, or symptom patterns. Among those I have encountered, the following are worth mentioning.

A 22-year-old young man had been complaining ever since his childhood of memory weakness, manifest in remembering both episodic events (he had to write down errands when he went shopping) and schooling (he failed to learn historical and geographic facts, mathematical formula, poetry and songs, and even the most common verbal series, such as alphabet letters and month names). Pregnancy and delivery were uneventful and he did not suffer from any disease in childhood. The neurological exam and other investigations were negative, except for a mild dyslexia. The syndrome remained unmodified throughout his life and was confirmed by his defective performance on a battery of memory tests, while no evidence of other cognitive defects emerged. With Lucchelli, we proposed to consider him an example of developmental dysmnesia.

Following an episode of encephalitis, a 44-year-old lady showed an amnesic pattern, which was the mirror image of that found in classic amnesia, namely, preserved autobiographic memory (thoroughly comparable to that of her husband) and severely impaired semantic memory. Word meaning as well as the stock of acquired knowledge, inclusive of nonverbal notions, such as monuments and recipe ingredients, were no longer

retrievable. The episodic-semantic dichotomy receives strong support from the evidence of double dissociation.

Their peculiarities notwithstanding, these and comparable cases fall by full right within the province of organic amnesia and do not call into question its conceptual scaffolding. Much more contentious and difficult to reconcile with the current body of knowledge on amnesia are patients who show a striking retrograde memory deficit with integrity of anterograde memory, in the absence of any evidence of brain damage. They have been repeatedly reported over the last 25 years and I had the opportunity to investigate three of them. The most common event associated with the onset of amnesia is a minor head trauma, not accompanied by loss of consciousness. It leaves the patients bereft of their past episodic and sometimes even semantic memories for a variable period of time (up to the entire span of life), without, however, impairing their ability to retain new information. The first idea that occurs to doctors, when they are confronted with patients complaining of a loss of function having idiosyncratic features and lacking evidence of a somatic lesion, is to look for events or conditions that may justify a psychological block. Sometimes they are easy to find and suggest either a voluntary mechanism that leads the patient to feign a morbid state to evade responsibility in a difficult state of affairs or an involuntary functional inhibition that relieves the patient from distressful emotions. It has rightly been recommended not to stop at the early negative evidence but to pursue with great tenacity a careful psychological investigation on the patient's history and present condition. However, what should be done if no direct or indirect support is gathered for a voluntary or involuntary psychic mechanism, as has happened with most reported cases? A few authors warn us never to yield to apparently negative findings, because a psychological cause must be there and its discovery is simply a question of time and determination. I am unconvinced by what seems to me a *petitio principii* that begs the question and I would plead for a more flexible approach, keeping a wait-and-see attitude, to collect new cases and for the time being to label these patients' amnesia functional, an adjective that stresses the loss of function but leaves its cause uncommitted.

When I reached 70, I retired from clinical and teaching commitments and for the next 5 years I devoted my time to research and the job as editor of *Cortex*. In 2000, this phase also came to an end and the role of chief editor of *Cortex* was handed over to the skillful hands of Sergio Dalla Sala, whose energies and spirit of enterprise have been decisive in renewing and enriching the journal.

As it sometimes happens, the end of my career was celebrated by the awarding of a few academic titles and honors. I was particularly flattered by the honorary degree in psychology awarded to me by the University La Sapienza of Rome. I saw it as an acknowledgment of the contribution that, profiting by the openings made by disease, other neurologists and

I gave to penetrating the recesses of mind, joining psychologists in what remains their main task. I see no competition between the two specialties, especially in a country, like Italy, where many of the psychologists now engaged in neuropsychological research have a neurological background.

Last December I celebrated my 80th birthday, in good health and with a mind, which has not, as far as I can judge, deteriorated beyond the physiological norm. I still wish to be kept abreast of what is happening around me and in the world, although I am not sure to always understand all of its implications. At my time of life people indulge in taking stock of their life and reconsidering its pros and cons. My survey is positive, not so much because of my merits but because fortune has protected me against what are called the blows of destiny, those unpredicted and uncontrollable events that upset the development of your projects and force you to make deleterious choices. I might even go as far as to say that I have been a lucky person, who has led the life he has wished and has drawn elements of satisfaction and comfort from his family and his job. That the kind of work I was doing was rewarding must be an impression I transmitted firmly to my children, because all of them chose to undertake an academic career, although not in the medical area.

As I mentioned at the beginning, the decision to study medicine was not my first choice, but came at the end of a period of uncertainties and second thoughts and was at least in part the fruit of a particular historical climate. It might have turned out to be a choice unsuited to my aptitudes or not completely up to scratch with respect to my aspirations. With the benefit of hindsight, I can say that it was wise and gratifying both intellectually and emotionally. I was able to combine the satisfaction of investigating one of the most intriguing areas of research, the structure of mind, with the wealth of social and emotional experiences linked to the medical profession. Yet precisely because my work was so absorbing, I had to neglect subjects outside the natural science area, which had attracted me so keenly in my youth when I thought they would have sharpened my understanding of what humans represent in the world. It is for this reason that when I retired, I opted for a complete change of cultural horizons, turning from science to history and poetry, mainly of the 20th century. My passion for history springs from different sources. Admittedly one of them is the well-known tendency of elderly persons to recall and ponder on their own past, inclusive of the experiences connected with public events. There is also the curiosity to know the truth and details about events that had made a huge impact on contemporaries and were the subjects of ongoing questions. However, a deeper and more enthralling motive is to gain a comprehensive view of the chain of events and underlying forces that have marked the great and terrible century (especially its first half) we have gone through. It is not that I expect my reading about the recent past to improve my understanding of the mechanism steering history or the design imminent to it

(which I believe does not exist), but because memory of what happened and of how we and our fathers behaved in those terrible contingencies should never be forgotten, if coming generations are to live in a decent world. Among the several warnings to emerge from the history of the past century, two seem to me particularly important. One is that, considering the present development of technology and the fierce awareness people have of their own rights, neither social conflicts nor disputes between nations have the least probability of being settled by using the force of weapons. All that will result is blood, mourning, and hate, with a dire incongruity between aims and results. The other is that whenever we become aware that a minority is abused in the name of majority's common feelings, we ought to voice our unyielding disapproval.

As to the charm of poetry, any comment on my part would be conceited. I only wish to point out that, however different the attitudes with which poets and scientists look at the world, they share the same will to bring to light aspects of reality that are concealed beneath the surface of things. To define the work of poets, Nafisi said that what they depict is not reality but an epiphany of truth. I like this distinction if truth is taken as a term referring to how the outer world is echoed by our sentiment and imagination and reality to the external world in its objective terms.

Selected Bibliography

Barbieri C, De Renzi E. The executive and ideational components of apraxia. *Cortex* 1988;24:535–543.

Borghi G, De Renzi E. Contributo alla conoscenza delle sindromi vascolari da rammollimento nell'ambito della silviana profonda. *Neurone* 1953;1:32–49.

De Renzi E. Il test di Rorschach negli schizofrenici di data recente. *Riv Sperim Freniatria* 1955;79:3–62.

De Renzi E. Il contributo del test di Rorschach nella diagnosi differenziale fra psicastenia e schizofrenia. *Lavoro Neuropsich* 1956;19:1–14.

De Renzi E. *Disorders of space exploration and cognition.* Chichester: John Wiley, 1982.

De Renzi E. Current issues on prosopagnosia. In Ellis HD, Jeeves MA, Newcombe F, Young A, eds. *Aspects of face processing.* Dordrecht: Nijhoff, 1986;243–252.

De Renzi E. Visuo-spatial disorders. In Kennard C, Clifford Rose F, eds. *Physiological aspects of clinical neuro-ophtalmology.* London: Chapman and Hall, 1988;155–171.

De Renzi E. What does psychogen mean? *Cortex* 2002;38:678–681.

De Renzi E, Barbieri C. The incidence of the grasp reflex following hemispheric lesion and its relation to frontal damage. *Brain* 1992;115:293–313.

De Renzi E, Cavalleri F, Facchini S. Imitation and utilization behavior. *J Neurol Neurosurg Psychiatry* 1996;61:396–400.

De Renzi E, Colombo A, Faglioni P, Gibertoni M. Conjugate gaze paresis in stroke patients with unilateral damage. *Neurology* 1982;39:482–486.

De Renzi E, Faglioni P. Normative data and screening power of a shortened version of the Token Test. *Cortex* 1978;14:41–49.

De Renzi E, Faglioni P, Grossi D, Nichelli P. Apperceptive and associative forms of prosopagnosia. *Cortex* 1991;27:213–221.

De Renzi E, Faglioni P, Lodesani M, Vecchi A. Impairment of left brain-damaged patients on imitation of single movements and motor sequences. Frontal- and parietal- injured patients compared. *Cortex* 1983;19:333–343.

De Renzi E, Faglioni P, Previdi P. Spatial memory and hemispheric locus of lesion. *Cortex* 1977;13:424–433.

De Renzi E, Faglioni P, Scotti G. Judgment of spatial orientation in patients with focal brain damage. *J Neurol Neurosurg Psychiatry* 1971;34:489–495.

De Renzi E, Faglioni P, Sorgato P. Modality-specific and supramodal mechanisms of apraxia. *Brain* 1982;105:301–312.

De Renzi E, Faglioni P, Villa P. Topographical amnesia. *J Neurol Neurosurg Psychiatry* 1977;40:498–505.

De Renzi E, Gatti B. La personalità sociopatica alla luce della indagine psicodiagnostica. *Arch Psicol Neurol Psichiatria* 1958;19:1–50.

De Renzi E, Gentilini M, Barbieri C. Auditory neglect. *J Neurol Neurosurg Psychiatry* 1989;52:613–617.

De Renzi E, Gentilini M, Faglioni P, Barbieri C. Attentional shift towards the rightmost stimuli in patients with left visual neglect. *Cortex* 1989;25:231–237.

De Renzi E, Gentilini M, Patacini F. Auditory extinction following hemisphere damage. *Neuropsychologia* 1984;27:733–744.

De Renzi E, Isotti M, Saraval A. Il test di Rorschach nell'italiano adulto normale. *Arch Psicol Neurol Psichiatria* 1957;18:279–321.

De Renzi E, Lucchelli F. Ideational apraxia. *Brain* 1988;111:1173–1185.

De Renzi E, Lucchelli F. Developmental dysmnesia in a poor reader. *Brain* 1990;113:1337–1345.

De Renzi E, Lucchelli F. Dense retrograde amnesia, intact learning capability and abnormal forgetting rate: A consolidation deficit? *Cortex* 1993;29:449–466.

De Renzi E, Lucchelli F. Are semantic systems separately represented in the brain? The case of living category impairment. *Cortex* 1994;30:3–25.

De Renzi E, Lucchelli F, Muggia S, Spinnler H. Persistent retrograde amnesia following a minor trauma. *Cortex* 1995;31:531–542.

De Renzi E, Lucchelli F, Muggia S, Spinnler H. Is memory loss without anatomical damage tantamount to a psychogenic deficit? The case of pure retrograde amnesia. *Neuropsychologia* 1997;35:781–794.

De Renzi E, Motti F, Nichelli P. Imitating gesture. A quantitative approach to ideomotor apraxia. *Arch Neurol* 1980;37:6–10.

De Renzi E, Perani D, Carlesimo G A, Silveri MC, Fazio F. Prosopagnosia can be associated with damage confined to the right hemisphere. An MRI and PET study and a review of the literature. *Neuropsychologia* 1994;32:893–902.

De Renzi E, Pieczuro A, Vignolo LA. Ideational apraxia. A quantitative study. *Neuropsychologia* 1968;6:41–52.

De Renzi E, Saetti MC. Associative agnosia and optic aplasia: Qualitative or quantitative difference? *Cortex* 1997;31:115–130.

De Renzi E, Scotti G. The influence of spatial disorders in impairing tactual discrimination of shapes. *Cortex* 1969;5:53–62.

De Renzi E, Spinnler H. Facial recognition in brain-damaged patients. *Neurology* 1966;16:145–152.

De Renzi E, Spinnler H. Impaired performance on color tasks in patients with hemispheric damage. *Cortex* 1967;3:194–217.

De Renzi E, Vignolo LA. The Token Test: A sensitive test to detect receptive disturbances in aphasics. *Brain* 1962;85:665–678.

De Renzi E, Zambolin A, Crisi G. The pattern of neuropsychological impairment associated with left posterior cerebral artery infarcts. *Brain* 1987;110: 1099–1116.

Gentilini M, Barbieri C, De Renzi E, Faglioni P. Space exploration with and without the aid of vision in hemisphere-damaged patients. *Cortex* 1989;25:643–651.

Saetti MC, De Renzi E, Comper M. Tactile morphagnosia secondary to spatial deficits. *Neuropsychologia* 1999;37:1087–1100.