Neural Grafting in the Mammalian CNS
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Intracerebral Neural Grafting: A Historical Perspective

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I. Introduction

During the last decade there has been an interesting trend in experimental brain research to go back to problems and issues that were formulated and pursued around the turn of the century. The last decades of the last century and the early decades of the present century was a golden era of what we today call neuroscience when many fundamental neurobiological questions were attacked experimentally for the first time. In retrospect, when going back to this early literature, one feels that the questions were often very well formulated but that in many respects the technology available was unable to provide the answers. The recent rapid development of powerful analytical tools and new methods for the study of the nervous system, therefore, has allowed our generation of researchers to 'rediscover' many of the clever experimental approaches and concepts of our forerunners.

This is certainly true of present-day research on neural plasticity and development. We owe much to the original work associated with the development of the neuron concept (by above all Ramón y Cajal and his contemporaries) for the formulation of many of those central concepts – such as trophism, tropism, guidance, specificity and neuron–glia interaction – which are in the focus also of current research on development and growth of neurons. Many of the early attempts at neural grafting were generated and designed with such basic questions in mind. By the end of the 19th century

and the early part of this century neuroscientists were certainly very open minded about the plasticity of nervous tissue and the modifiability of the neuron, its shape and its connectivity. It is relatively recently that we have come back to a similar open-mindedness in the way we experimentally approach these problems. It is interesting, therefore, to see how experimental strategies adopted also in current intracerebral neural grafting research fall back on attempts made during the early decades of this century.

II. Early History

In Table I we have tried to identify some key publications in the early history of intracerebral neural grafting in mammals. This research has a tradition that goes back to Thompson (1890), Forssman (1898, 1900) and Saltykow (1905). These studies were made with different questions in mind. Thompson was interested in the general transplantability of brain tissue. He exchanged large pieces of neocortical tissue between adult cats and dogs and had some of the grafts analyzed microscopically after survival times of up to seven weeks. Despite that his long-term grafts probably consisted solely of neuron-free graft remnants and developing scar tissue, Thompson was remarkably pleased with his results, as reflected in the title, 'Successful brain grafting', and his conclusion has a slightly prophetic tone:

> 'I think the main fact of this experiment – namely that brain tissue has sufficient vitality to survive for seven weeks the operation without wholly losing its identity as brain substance – suggests an interesting field for further research, and have no doubt that other experimenters will be rewarded by investigating it'.

The work of Saltykow and Forssman was chiefly generated by an interest in two questions which have remained in the focus of neural grafting research, namely the transplantability and regenerative capacities of CNS tissue, on the one hand, and the ability of such tissue to stimulate neuronal regeneration, on the other. In Saltykow's experiments on reimplantation of conically shaped pieces of neocortex in young adult rabbits the implants were totally resorbed and slowly replaced by what seemed to be a vessel-rich connective tissue surrounded by a glial scar. Forssman was the one who introduced the concepts of neurotropism and chemotropism in the guidance of regenerating peripheral nerves. As part of his experiments on neurotropism he implanted brain tissue from young adult rabbits into tubes of straw or collodium which he sutured onto the proximal stumps of cut peripheral nerves in different arrangements. Although there was no sign of any long-term survival of the implanted brain tissue he reported that the implants

TABLE I

EARLY HISTORY OF NEURAL GRAFTING IN THE MAMMALIAN CNS

1890 - W.G. THOMPSON (New York, U.S.A.)	First attempt to graft adult CNS tissue to brain
1898 - J. FORSSMAN (Lund, Sweden)	First report of neurotropic effects of grafted CNS tissue
1907 - G. DEL CONTE (Naples, Italy)	First attempt to graft embryonic tissues to brain
1909 - W. RANSON (Chicago, U.S.A.)	First successful grafting of spinal ganglia to brain
1911 - F. TELLO (Madrid, Spain)	First successful grafting of peripheral nerve to brain
1917 - E. DUNN (Chicago, U.S.A.)	First successful grafting of neonatal CNS tissue to neonatal brain
1921 - Y. SHIRAI (Tokyo, Japan)	First demonstration of brain as an immunologically priviliged site
1924 - G. FALDINO (Pisa, Italy)	First successful grafting of fetal CNS tissue to anterior eye chamber
1940 - W.E. LE GROS CLARK (Oxford, U.K.)	First successful grafting of fetal CNS tissue to neonatal brain
1957 - B. FLERKÓ and J. SZENTÁGOTHAI (Pécs, Hungary)	First successful intraventricular grafting of endocrine tissue
1970 - 1972	First reports of reliable grafting to brain and anterior eye chamber

had a strong neurotropic action on the regenerating axons, similar to what he saw with implants of peripheral nerve:

> 'Die Kraft, welche die Nervenfasern in das mit Gehirnsubstanz gefullte Röhrchen treibt, habe ich Neurotropismus genannt, und ich war geneigt, dieselbe als einen Art Chemotropismus zu betrachten. Welchen chemischen Stoffen oder welche Combinationen von solchen in dieser im Zerfall befindlichen Substanz die attrahierende Eigenschaft zukommt, daruber hatte ich dazumal und habe auch jetzt keine Meinung. (The force which drives the nerve fibers into the tubes filled with brain substance I have named neurotropism, and I was inclined to regard this as a form of chemotropism. Which chemical substances or combination of substances possess this attracting property in the disintegrating tissue I had then, and I have also now, no opinion about).'

In his second paper, from 1900, Forssman described that this effect was specific for nervous tissue and that it did not occur with similar implants of tissue from liver or spleen.

Tello (1911), apparently inspired by earlier but less successful experiments by Lugaro (1906), was the first to report successful grafting of pieces of peripheral nerve into the depth of the brain. Based on the earlier demonstrations of growth stimulating effects of peripheral nerve on regenerating peripheral axons, Tello grafted pieces of predegenerated peripheral nerve into the cerebral cortex in adult rabbits with the aim of studying the ability of such grafts to stimulate or attract regenerating central fibers. From his observations on silver-stained specimens he concluded that this was indeed the case. Tello's observations were later followed up in a number of studies with widely varying results (see, e.g., Shirai, 1935; Sugar and Gerard, 1940; Le Gros Clark, 1942; Barnard and Carpenter, 1950; Feigin et al., 1951; Glees and Erikson, 1953; Horvat, 1966). Le Gros Clark, in particular, was of the opinion that the intracerebral nerve grafts were reinnervated from peripheral nerves in the meninges and the scalp rather than from fibers originating in the damaged brain substance. Thus, the central origin of the fibers seen to extend into grafts of peripheral tissues in the silver-stained preparations of Tello and others remained highly controversial until the 1970s when modern histochemical methods and tract-tracing techniques have been able to furnish definitive proofs for Tello's early interpretations.

The features of the mammalian brain as a transplantation site were first explored by Del Conte in 1907. He grafted a variety of non-neural embryonic tissues which he inserted by means of a pair of forceps into the cerebral cortex of adult dogs. He observed partial survival of some tissues – such as cartilage, connective tissue and pituitary tissue – while others were totally resorbed. He felt that graft survival was only temporary, above all due to lack of growth space, and concluded that the brain was an unfavorable implantation site for most types of embryonic tissues.

This approach was further pursued, and with considerably better results,

by Willis in 1935. He implanted various types of tissues from rat embryos into the depth of the cerebral hemisphere in two weeks to four months old recipient rats. The fetal tissue was implanted as small (about 0.2 mm) fragments by means of a lumbar puncture needle equipped with a plunger, a technique which seems to have been introduced by Murphy and Sturm (1923) for intracerebral grafting of tumors (see below). Willis' grafts, which mostly consisted of minced whole body parts, survived and grew very well, but he saw no traces of surviving neural tissues. He concluded that the brain was a particularly favorable site for the transplantation of many types of embryonic tissues.

In 1907 Nageotte, and Marinesco and Minea, had reported successful grafting of neonatal or adult ganglia under the skin of adult mammals. Shortly thereafter, Ranson (1909, 1914) tried the same experiment to the brain in rats. He obtained partial survival of sensory neurons in spinal ganglia, taken from neonatal donors, after grafting into the cortex of young adult recipients. Tidd (1932) later showed that good survival of ganglionic neurons could also be obtained when taken from young adult (one month old) rat donors.

Dunn was the first to demonstrate, in 1917, that CNS tissue could be made to survive in the brain provided that the graft tissue is in an immature, developing state. She took wedge-shaped pieces of cortical tissue from 9–10-day-old rat pups and grafted them into cortical cavities of the same shape in other pups of the same litters. Her survival rate was poor, less than 10%. She apparently struggled with this material over many years, starting the experiment already in 1904, and in her paper she reports on a total of 44 specimens, out of which four showed some degree of survival. In summarizing her experience she states that:

> 'The two points of chief importance in successful cerebral transplantation are first, the retention in place of the material transferred, and second, the furnishing to it of an adequate blood supply . . . In my own successful operations the transplanted portions have remained adherent to the denuded portions of the cortex but have taken some position near the choroid plexus of the lateral ventricle and have apparently received their blood supply from that source'.

Dunn's best grafts of neonatal cortex, although small in size, had retained their features of cortical tissue and showed some degree of lamination of their constituent neurons.

This work was to be followed up by Le Gros Clark (1940) and Glees (1940, 1955) using fetal cortical tissue as grafts. They addressed the question of how pieces of mammalian CNS tissue can develop, grow and differentiate outside its normal context. Le Gros Clark was inspired by Willis' (1935) report of the brain as a highly favorable transplantation site for embryonic tissues, and by

the reports by Waterman (1932) and Nicholas and Rudwick (1933) of excellent survival and differentiation of eye primordia grafted to the omentum in rabbits, and of rat neuroectoderm grafted to the chick chorio-allantoic membrane, respectively. Prior to them, also Faldino (1924) and May (1930) had shown that mammalian CNS tissue could be transplanted, in their case to the anterior eye chamber, provided that it was taken from fetal donors.

In comparison with Dunn's relatively poor results with intracortical cortical grafts from neonatal donors, the impression from both Le Gros Clark's and Glees' reports is that the fetal grafts demonstrated better survival, growth, neuronal differentiation and intrinsic laminar organization. But none of these studies were able to demonstrate any crossing between the graft and the host, and these authors felt that the grafts developed in relative isolation from brain of the host. Le Gros Clark viewed his results in the context of experimental neuroendocrinology:

> 'The experiment recorded in this paper demonstrates the viability of cortical neuroblastic tissue which has been implanted into the brain of a young animal. It also demonstrates its capability for continued growth and differentiation . . . It thus appears that the differentiation of cell-types can occur independently of the normal connections of the cortex with other parts of the central nervous system, and this is possibly also the case with their organization into the characteristic cortical laminae'.

It is remarkable that this work was never followed up, and it is notable that Le Gros Clark in his autobiography from 1968 does not even mention this work. It was not until the last decade that these kinds of experiments were tried again, which led to the discoveries, first, in 1976, that grafts of developing CNS tissue can establish extensive afferent and efferent connections with the (developing or mature) host brain, and then, in 1979, that these connections could be both electrophysiologically and behaviorally functional.

Shirai (1921) and Murphy and Sturm (1923) were probably the first to study intracerebral grafts from an immunological standpoint. Their observations on the survival of xenogenic tumor grafts have subsequently led to the concept of the brain (like the anterior eye chamber) as an immunologically privileged site (Medawar, 1948; Greene, 1953; see Mason et al., this volume). Murphy and Sturm (1923), who were the first to use the technique of injecting the transplant into the brain by means of a cannula, reported that cross-species tumor grafts survived as well as homologous ones, but that the exact site within the brain seemed to play a role:

> 'In confirmation of Shirai's observation we find that transplantable mouse tumors grow actively when inoculated into the brains of rats, guinea pigs, and pigeons, whereas subcutaneous or intramuscular grafts in the same animals fail. The growth of foreign tissue in the brain, moreover, takes place only when the grafted material lies entirely in the brain tissue; if

it comes in contact with the ventricle a cellular reaction takes place with resultant destruction of the graft. The growth of foreign tissue in the brain may be completely inhibited by simultaneous inoculations of a small bit of autologous but not by a bit of homologous spleen tissue'.

Greene and Arnold (1945), working with grafts to the anterior eye chamber, later showed that these conclusions were applicable also to normal fetal CNS tissue, and they were probably also the first to report successful grafting of human brain tissue:

'The transplantation of rabbit and human embryonic brain to the anterior eye chambers of guinea pig eyes also gave rise to a high percentage of takes with progressive growth comparable to that obtained in the homologous transfer . . . Pigs bearing human brain were followed for more than two years without the appearance of regressive changes and there is no reason to believe that the transplants would not persist throughout the life of the alien host'.

Greene and Arnold's (1945) paper also contains one of the most curious passages we have come across in the neural grafting literature, with a bearing on current interest in ethical aspects on neural grafting:

'The existence of human brain in lower animals also excites speculation from a purely philosophical standpoint. On the assumption that the human brain is the seat of the intellect, some alteration might be expected in the behavior of guinea-pigs bearing such transplants. However, observation has shown no change suggestive of higher faculties. In fact, the only variation differentiating a guinea pig bearing a human brain from a normal pig is a marked increase in libido'.

Flerkó and Szentágothai (1957) and Halász et al. (1962) were the first to report successful grafting to the brain ventricles. They implanted stereotaxically (using an injection technique with a cannula) endocrine tissue (ovary or pituitary) into, or in the immediate vicinity of, the third ventricle. This approach has more recently been successfully used also for grafts of peripheral and central nervous tissue by Rosenstein and Brightman (1978) and Perlow et al. (1979). Interestingly, the experiments of Halász et al. (1962, 1963, 1965) also furnished the first evidence of a functional host–graft interaction. Thus, the cells of the intracerebral pituitary grafts developed normal stainability and hormone secretion only if they were placed in association with the so-called hypophysiotrophic area of the mediobasal hypothalamus (and not elsewhere in the brain), where they could be influenced humorally by hypophysiotrophic hormones released by the host hypothalamic neurons. Indeed, in such a position the intrahypothalamic pituitary grafts could compensate for several of the endocrine deficits seen in hypophysectomized rats (Halász et al., 1963, 1965).

III. Recent Developments

The recent history of neural grafting dates back to the early 1970s, when three different laboratories (Das and Altman, 1971, 1972; Olson and Malmfors, 1970; Olson and Seiger, 1972; Björklund and Stenevi, 1971; Björklund et al., 1971) introduced new autoradiographic and histochemical methods to the study of grafted tissues. This revival does not seem to have been inspired by any awareness of the previous tradition of intracerebral neural grafting, surveyed above. With some singular exceptions – such as Tello's, Sugar and Gerard's and Le Gros Clark's papers on regeneration into peripheral nerve grafts, which have remained well known in the regeneration literature – the early papers became buried in the archives. Thus, for many now active workers it has been a pleasant surprise to rediscover the early work and realize that several of the fundamental neurobiological phenomena and experimental paradigms attacked in current research have previously been conceptualized and addressed by the early workers in the field.

One can wonder why so few of the interesting early findings and experimental models were really followed up. One reason is probably that the overall impression of the feasibility to graft neural tissues to the CNS of mammals was quite negative in the literature published before the 1970s. This was of course the case in Saltykow's (1905), Del Conte's (1907) and Willis' (1935) studies, quoted above, but also in a number of other papers published over the years, in particular Altobelli (1914), Sugar and Gerard (1940), Barnard and Carpenter (1950), Glees (1955), Wenzel and Bärlehner (1969) and Frotcher et al. (1970). Also Dunn's (1917) pioneering work showed in fact only very limited success. Thus, although some of the early studies can be said to have shown that survival of intracerebrally grafted peripheral and central nervous tissue could be achieved in mammals, it was not until the 1970s that the conditions for good and consistent survival of intracerebral grafts in developing and adult recipients were defined.

Another reason is probably that neural grafting turned out to be technically so much easier in cold-blooded vertebrates. Thus, starting in the 1920s, transplantation, reimplantation, or transposition of CNS tissue in urodeles, amphibians and fish have provided powerful experimental models, some of which have become classical aproaches for the study of development and regeneration in the nervous system. Neural grafting models in submammalian vertebrates have of course played a major role in the development of modern concepts on the specificity and mechanisms of formation of neuronal connections. This work developed very much in parallel with the various attempts at neural grafting in mammals dealt with here; it attracted inevitably much more interest, and it has probably also played a much greater role as a source of inspiration for the revival of neural grafting in mammals. It was

originally thought that the remarkable regenerative and functional potential of CNS tissue grafts - e.g. in the retinotectal system and the spinal cord in newts, frogs and fishes - reflected a fundamental difference in the regenerative properties of central nervous tissue between cold-blooded vertebrates and mammals. It is only during the last few years that it has become evident that this is indeed not the case and that at least certain types of intracerebral neural grafts can perform just as well in developing and adult mammals as in developing or adult submammalian vertebrates.

This conceptual change stands out as one of the most significant aspects of the recent developments in the neural grafting field. The realization that the mammalian central nervous system has a high capacity to incorporate and interact with implanted neuronal and glial elements and that such implanted elements can modify the function and behavior of the host has opened new exciting perspectives for future work. It has also been an impetus for new ideas and new approaches where the intracerebral grafting technique is used as a new tool to analyze a wide variety of problems in current neuroscience research. This trend is reflected in the chapters included in this volume, and it can also be observed in the annual publication curve included in the Bibliography at the end of the book (Chapter 59), which shows that, in 1983 alone, as many papers were published on neural grafting in mammals as in the whole century preceeding 1970.

In closing the present survey, we recently came across the following quotation of old wisdom, which may have been inspired by the emerging modern physical science, but which may just as well have been phrased by a modern neural grafting scientist*:

> 'Whenever a new discovery is reported to the scientific world they say first. 'It is probably not true'. Thereafter, when the truth of the proposition has been demonstrated beyond question, they say. 'Yes, it may be true, but it is not important'. Finally, when sufficient time has elapsed to fully evidence its importance they say. 'Yes, surely, it is important, but it is no longer new'.'

Thus, although we have to admit that much of what is being pursued in current neural grafting research is not entirely new, we can be pleased to know that it is important!

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*This quotation from Michel de Montaigne (1553-1592) was taken from G. Jaim-Etcheverry, Trends Neurosci., May, 1984.

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