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The National NeuroAIDS Tissue Consortium: a new paradigm in brain banking with an emphasis on infectious disease

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The National NeuroAIDS Tissue Consortium: a new paradigm in brain banking with an emphasis on infectious disease

The National NeuroAIDS Tissue Consortium (NNTC) was founded in 1998, in response to the scientific need for well-characterized central nervous system (CNS) and peripheral nervous system (PNS) tissues and fluids from HIV-infected individuals. In addition to performing the routine functions of non-transplant anatomic tissue banks, the Consortium offers a unique model for the integration of independent research entities in order to provide well-characterized tissues and fluids for the international research community. Herein, we describe the structure of the Consortium, pointing out the inherent strengths of linking together multiple independent sites for the purpose of banking HIV-infected nervous system tissues. We describe the neuropathology protocol that was adopted and successfully implemented at the four participating banks of the Consortium.

Keywords: AIDS, brain bank, HIV

Introduction

Well-characterized human brains have great utility in studies of HIV neuropathogenesis and studies relating to adequate treatment aimed at eliminating CNS viral reservoirs. Despite their importance in the ultimate validation of current treatment regimens and theories of disease, there have been no major American efforts to provide systematic mechanisms for infectious specimen accrual and distribution, and we are aware of only two European brain banks with a focus on HIV-related disease [2,4]. In contrast, well-developed worldwide brain banks with emphases on non-infectious, neurodegenerative and demyelinating disorders have become an important resource for the neuroscience community [12]. The reasons for this may be multifactorial: the perceived difficulty and risk in handling infectious materials discourages *post-mortem* services from acquiring specimens [8]; collections serving the needs of localized NeuroAIDS research communities have been extant for over a decade [7,9]; the volume of

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these autopsies is decreasing with improvements in antiretroviral therapies and enhanced patient survival [10,13]; and the general rate of autopsies has declined with a lack of incentives to clinical faculty for their procurement [14].

An effective resource for infectious nervous system tissues and fluids should be capable of providing to all qualified investigators, regardless of geographical site or academic affiliation, uniformly characterized, high quality and relatively abundant specimens with a minimum delay and in a safe manner. In spite of the impediments to the banking of infectious, and in particular HIV-infected, materials, the National NeuroAIDS Tissue Consortium (NNTC) has implemented a model for a cooperative brain bank specializing in infectious diseases. One and a half years after its inception, the Consortium has provided specimens and clinical information to a wide variety of investigators, despite the dramatic decreases in AIDS-related mortality that began in 1996.

Structure of the National NeuroAIDS Tissue Consortium

The structure of the NNTC is unique with regard to brain banks worldwide. Currently, there are four tissue banks participating in the NNTC, located in Galveston, Texas, Los Angeles, California, New York, New York and San Diego, California. These entities are funded through resource (R24) grants from the National Institutes of Health (NIH), giving them simultaneous mandates to become resources for the general HIV neuroscience community and to conduct site-specific and collaborative research into neurologic, neuropsychologic and neuropathologic manifestations of HIV infection. The Consortium is managed by a steering committee composed of the principal investigators from the four sites (two of whom are neuropathologists, one a neurologist and one a psychiatrist), representatives from the NIH institutes (Mental Health, Neurologic Disease, and Drug Abuse), and expert advisors selected by the NIH. The NNTC Steering Committee oversees all linked functions of the Consortium, and is responsible for approval and implementation of all protocols shared among sites. Through monthly teleconferencing and tri-monthly meetings of this body, the NNTC has been able to coordinate its activities in conducting clinical studies and acquiring and uniformly characterizing tissue and fluid specimens.

An External Advisory Board to the NNTC Steering Committee was created by the NIH to review the progress of the Consortium on an annual basis. The external Board is composed of experts in HIV-related neurologic, neuropsychologic and neuropathologic disorders, patient welfare advocates and authorities in non-transplant anatomic banking. The NNTC Steering Committee considers the annual recommendations of the Advisory Board, and chooses to alter or maintain its policies accordingly, with formalized rationales for its decisions.

Three subcommittees report to the NNTC Steering Committee, in the following disciplines: neuropathology, neurology/medicine and psychology/psychiatry. These groups were assembled from experts at each of the NNTC sites, and were charged with developing uniform protocols to evaluate study subjects and process tissues and fluids. Subcommittee members also participate in a rigorous programme of intersite quality assurance implemented by the Consortium.

A national coordination office has also been established and reports to the Steering Committee; its function has largely been as an informational outlet for the NNTC, and it assists and facilitates outside investigators in their acquisition of specimens and information. It maintains phone lines (+1-800-510-1678, +1-718-494-5161), a fax line (+1-718-494-5347) and a website (http://www.hivbrainbanks.org). A centralized NNTC database is also in progress, and will contain critical information on patient and specimen characteristics to be used both by the Consortium and by outside investigators.

The Consortium structure described above is unique, and has been established for the primary purpose of cooperative brain banking to provide all qualified investigators with uniformly obtained and characterized specimens and clinical information. We are unaware of a similar endeavour in any aspect of human-based tissue research, as most brain banks function independently or as components of specific institutional programme projects and centres. While the National Disease Research Interchange (NDRI) organizes the procurement of human tissues and fluids across many centres, there is no attempt to standardize the clinical characterization of subjects contributing specimens at any of the NDRI's participating sites [11]. While multicentre brain banking research groups exist, their prime purpose has been for internally driven research, and not as a generalized research infrastructure. The strengths of the NNTC structure are the following: it can generate large

numbers of uniformly characterized specimens in a short period of time, it can provide outside investigators with extensive and uniform clinical data on patients under study, it is responsive to individual member banks through their participation in the steering committee, and its resources can be utilized in Consortium-initiated and individual site-initiated research.

Clinical and laboratory evaluations

Subjects are recruited to study at the four participating NNTC sites on the basis of eligibility criteria indicative of advanced HIV disease, and willingness to participate in a *post-mortem* organ donation programme. Although the vast majority of patients are experienced with regard to antiretroviral therapies, a small subpopulation are treatment naïve or on structured treatment interruption. Both genders, all ethnicities and all risk groups are included; however, paediatric populations have to date been excluded from clinical analysis. Subjects are recruited to a longitudinal, observational study that includes detailed neurologic, neuropsychologic and psychiatric evaluations at 6-month intervals. These examinations have been standardized for use in all four sites and include batteries of neuropsychological tests, formalized algorithms for neurologic diagnosis, and a scripted interview (the Psychiatric Research Interview for Substance and Mental Disorders or PRISM [6]) for psychiatric diagnosis. During the course of the study, blood, urine and cerebrospinal fluid samples are obtained synchronously with the clinical evaluations. These fluids are both sent for laboratory analysis and are banked for the purposes of research requests. Study subjects are followed until the time of their death, and then rapid autopsies are performed.

The *pre-mortem* clinical analysis resembles other multicentre studies of disease, but is unique in these respects: (i) protocols were developed after the Consortium was formed; (ii) protocols were orientated towards the purpose of enhancing the value of the banking operations; (iii) testable medical hypotheses were not considered in their generation; and (iv) the correlation of *pre-* and *post-mortem* data was the major consideration in implementation.

Control subjects are obtained at the time of death from the *post-mortem* services through which Consortium members operate. These control tissues are obtained only after consent to *post-mortem*, and research documents are signed by the decedants' primary next of kin. Prospective clinical studies are not performed on these individuals.

Autopsy and neuropathology protocols

General

The value of tissue specimens is greatly enhanced by the maintenance of a short time interval between the patient's death and the processing of tissues because it minimizes protein and nucleic acid degradation. The implementation of rapid *post-mortem* protocols has followed local state and municipal requirements at each of the NNTC sites; many have chosen to use the Uniform Anatomical Gift Act to expedite the *post-mortem* upon the patient's demize [1]. This Act enables study participants to sign a legal document in which they can stipulate that, at their death, organ donation to the corresponding NNTC study be accomplished, without necessitating formal *post-mortem* permission from the primary next of kin. Thus, upon demize, given an appropriate interval for family and caregiver expressions of grief, the body can be transported to the *post-mortem* suite without the time-consuming necessity of requesting and completing a formal *post-mortem* permission document. In states where laws regarding anatomical gifts are more restrictive, participating sites have obtained rapid autopsies uniformly and successfully using standard authorization procedures [5].

While it was desired that the *post-mortem* interval be as short as possible, preferably under 24 h, there were no time limits in the Consortium for exclusion of brain specimens. It was acknowledged that autopsies with longer intervals from well-characterized individuals (i.e. those enrolled in a longitudinal study), although less useful in terms of molecular and virologic analysis, would maintain significant value by virtue of clinicopathologic correlation. An arbitrary goal of 70% was set for the number of autopsies occurring in year 1 that ideally would fall within the 24 h limit. This 24 h time interval represents the time from patient death to the freeze time for nervous system tissues. It was recognized that at some sites, the freeze time for brain might be prolonged by the acquisition of systemic, spinal and appendicular tissues. Thus, the judgement of the attending neuropathologist is important for determining the approach to be used in a given *post-mortem*. Some sites elect to recover all tissues

in one procedure; some perform a two-stage acquisition of tissues that produces different freeze times for brain and other tissues; and, in some, the collection protocol is abridged, resulting in fewer sampled sites but quicker freezing.

The minimal set of tissue types, and suggested quantities, that NNTC procures at *post-mortem* examination when complete *post-mortem* is obtained is displayed in Table 1. With regard to systemic tissues, the NNTC list is not meant to be comprehensive, but was developed as an expedient and generalized sampling of organs with relevance to the immunological and virological characterization of the patients. The banking sites are also encouraged to obtain portions of terminal ileum as a source of gut-associated lymphoid tissue, and eyes, although this is not mandatory. The NNTC list is a straightforward one, but differs from other protocols in its emphasis both on central and peripheral nervous system and skeletal muscular tissue. Carefully determined rationales for inclusion of specific peripheral nerves is as follows. The rationale for obtaining sural nerve is that it has been extensively studied by *pre-mortem* biopsy, and thus, has well-documented age normal distributions of fibre types and widely recognized involvement in various peripheral neuropathies. It is conveniently sampled because of its superficial location and the obvious external landmarks that are near it. It is preferred for *pre-mortem* nerve biopsy because it is predominantly sensory and cutting it causes no paresis and only a focal, minimal sensory deficit. The rationale for harvesting the common peroneal and branches is that, since neuropathies may be selectively motor and/or sensory, a sample of a motor nerve or a mixed nerve may be useful for comparison to the sensory (sural) nerve biopsy. As a mixed nerve, the common peroneal and its proximal branches offer some advantages. It is superficially located, giving ease of access. There is a large osseous landmark that allows it to be located easily. It has a thickness that is comparable to sural nerve samples and thus is optimal for plastic section or ultrastructural study. Finally, skeletal muscle sites were chosen with the rationale that both proximal and distal groups should be sampled, and should be accessible with a minimum of effort. Both vastus lateralis and gastrocnemius are accessible through the leg incisions made for acquisition of peripheral nerve. The peroneus longus muscle also is sampled at some sites for potential correlation with peroneal nerve pathology.

Brain dissection and storage

The brain is removed and weighed. Cerebrospinal fluid is aspirated after brain removal by needle and syringe through the floor of the third ventricle, or by direct aspiration from the lateral ventricles after the cerebral hemispheres have been separated in the mid sagittal plane. The entire brain (brain stem, cerebellum and cerebrum) is bisected longitudinally. A minimum of one half-brain is used for routine banking procedures. The other half-brain is processed in a manner to be determined by the

Table 1. List of tissues obtained from NNTC autopsies

Organ	*Amount acquired*
Brain	Entire organ
Pituitary gland	Entire gland
Spinal cord and attached dorsal root ganglia	Entire as approached from an anterior vertebrectomy. This results in a specimen from the cauda equina to the proximal thoracic or distal cervical cord.
Trigeminal ganglia	Both
Peripheral nerves	6 cm from each site i. sural ii. common peroneal and its branches
Skeletal muscle	2 g from each site i. proximal: vastus lateralis ii. distal: gastrocnemius
Spleen	1 cm slab dissected into 20-g minislabs
Lymph nodes (whichever are accessible)	Minimum of four
Liver	1 cm slab dissected into 20-g minislabs
Vertebral bone marrow	0.5–1.0-cm thick slice of one mid-thoracic body
Adipose tissue from abdominal incision	2 g

neuropathologists at the participating sites. At some sites, both halves are entered into the Consortium bank. At other sites, the neuropathologist's discretion is used to determine the uses of one of the hemispheres (such as medical resident training and diagnostic workups). When the entire brain is not entered into the bank, there is a notation in the bank catalogue that other, non-banked brain tissues exist from these cases. The catalogue may also describe the manner in which the non-banked hemisphere was handled (for example, frozen, fixed, slabbed, subdissected, etc.), and how it was used (for example, for stereotaxy, teaching, etc.). The catalogue also states that applicants interested in these non-routinely handled hemispheres should directly contact the individual sites.

Choosing which hemisphere is to be banked is left to the discretion of the site neuropathologist. Once this is determined, the brain stem and cerebellum are removed from the cerebral hemispheres by a cut through the rostral midbrain. The cerebral hemisphere is then coronally sliced at 0.8–1.0-cm intervals. Coronal slices are serially numbered (1, 2, 3, etc.). *DeArmond's Atlas of Neuroanatomy* is used to map these coronal sections to specific levels depicted in the *Atlas* [3]. For example, if the mamillary bodies are depicted in the seventh coronal level of the *Atlas*, and fall in the fifteenth slice of the bank brain, coronal slice 15 is identified as containing anatomic level 7. If two *Atlas*-depicted levels exist within one slice, that coronal slice will be identified by two anatomic level numbers (for example, if slice 15 contains mamillary bodies and anterior thalamic nucleus depicted in two *Atlas* levels, 15 would be identified as containing levels 6 and 7). The brain stem and cerebellum are sectioned in a horizontal (cross-sectional) manner at 0.5-cm intervals. Anatomic levels are again determined by comparison to *DeArmond's Atlas*.

All brain slices are photographed, either with a standard or digital camera. Routinely acquired images (with standard camera) are scanned into digital format. Digital images (either from the digital camera or flatbed scanner) are imported into a computerized database. The minimal resolution of these images is 640×480 pixels. Either all slices of the banked hemisphere are frozen, or alternating slices are either frozen and stored at -70°C or fixed in 10% phosphate-buffered formalin for between 12 and 24 h. If the sections are not completely fixed after that interval, the neuropathologist uses judgement in determining adequate fixation time. The freezing process must be rapid: that is, tissues are to be snap-frozen either in liquid nitrogen, or between two metallic (aluminium) plates that have been stored in a -70 to -80°C freezer or that are chilled in liquid nitrogen. Slices, in their bags with labels, are either lowered into the liquid nitrogen with tongs to which aluminium plates have been affixed, or are sandwiched between the prechilled plates, so that the slices freeze flat.

After fixation, blocks are cut from the fixed coronal/cross-sectional tissue slices, and processed for paraffin-embedding and routine histology. These blocks serve as the basis for the histological characterization of brains in the bank catalogues. Minimal and optional sectioning protocols are displayed in Table 2 and Figure 1. The non-blocked fixed coronal/cross-sectional tissue slices are then transferred to 0.1% phosphate-buffered formalin/0.01% sodium azide for storage.

Across all members of the Consortium, the only required stain for each sectioned tissue block is an haematoxylin and eosin (H&E). Some sites routinely perform immunohistochemistry for HIV p24 antigen, CD68 and glial fibrillary acidic protein (GFAP) on a subset of the sections. All sites perform special stains after an initial microscopic case review targets the appropriate selections. As the nature of the infectious, neoplastic, vascular and metabolic disorders seen with HIV is highly variable, the Consortium has elected not to mandate a panel of special stains, but to allow site neuropathologists discretion in the analysis of their materials. However, this decision is enforced with a quality control mechanism that assures appropriate analysis of materials (see below). Finally, records of all diagnoses are kept not only for each brain examined, but also for individual blocks. Global diagnoses are recorded in a central NNTC database, whereas information on individual blocks is stored at the individual brain bank sites.

Spinal cord dissection and storage

The spinal cord is blocked into 1–2-cm segments, which are alternatively fixed and frozen. The segments are serially numbered, starting from the conus as a uniform point. Alternating slices are either snap-frozen and stored at -70°C or fixed in 10% phosphate-buffered formalin for between 12 and 24 h. Spinal roots are treated according to the section to which they are attached – that is, fixed or frozen according to their originating segment. The dural sheath is used to maintain anatomic continuity

Table 2. Minimal and optional sectioning protocols for HIV-infected brains obtained by the NNTC

Protocol
Minimal
1. Frontal lobe: Middle frontal gyrus (Brodmann area 8), taken at the coronal level of the head of the caudate nucleus, with underlying white matter
2. Frontal lobe: Precentral gyrus, motor strip (area 4), taken at the coronal level of the mamillary body, with underlying white matter
3. Parietal lobe: Postcentral gyrus, sensory cortex (areas 1–3), taken at the coronal level of the splenium (where it is the superior-most gyrus of the hemisphere, before plunging into the interhemispheric fissure)
4. Parietal lobe: Angular gyrus (area 7), taken at the coronal level immediately posterior to the occipital horn of the ventricle
5. Temporal lobe: Middle hippocampus with lateral geniculate body and inferior temporal gyrus
6. Temporal lobe: Mid-superior and mid-middle gyri, same coronal level as section 8 (area 21–22)
7. Anterior basal ganglia: Caudate and putamen at anterior limb of the internal capsule
8. Posterior basal ganglia: Putamen, globus pallidus, internal capsule, claustrum, insula, and possibly anterior thalamus
9. Anterior cingulum: Corpus callosum, cingulate gyrus, extending around the angle of the lateral ventricle, at the coronal level of the anterior commissure
10. Anterior commissure, substantia innominata, and insula
11. Occipital lobe: Calcarine fissure with Genaris strip (areas 17–18)
12. Cerebellum: A hemispheric sample perpendicular to the folia to include dentate nucleus
13. Midbrain: Transverse slice to include substantia nigra
14. Pons: Transverse slice with a middle cerebellar peduncle
15. Medulla Oblongata: Transverse slice to include inferior olivary nuclei
Optional sectioning sites
16. Frontal lobe: White matter (centrum semiovale) deep to section 1, section to abut the angle of the ventricular system
17. Frontal lobe: White matter (centrum semiovale) deep to section 2, section to abut ventricle, likely to involve the body of the caudate
18. Parietal lobe: White matter (centrum semiovale) deep to section 3, to abut the ventricle
19. Optic nerve
20. Olfactory bulb
21. Pineal gland
22. Mammillary body/hypothalamus
23. Amygdala
24. Midthalamus (at coronal level of hippocampal sections)
25. Posterior thalamus (pulvinar)
26. Cerebellar vermis

for fixation (after opening the dura, the entire structure minus the frozen segments are placed in a long pan with fixative). At least four dorsal root ganglia are bisected for fixation and freezing. Minimal sections are obtained from lumbosacral, lower, mid and upper thoracic and, if possible, cervical levels.

Dissection and storage of peripheral nerves and skeletal muscle

Peripheral nerves The sural, common peroneal and its motor and sensory branches are sectioned perpendicular to their long axes for fixation and freezing. Then, 2.5 cm of either the sural or each nerve are fixed in glutaraldehyde for 24 h, by weighted suspension or by support on cardboard. After 24 h fixation, the nerves are stored either in PBS or cacodylate buffer. For fixed nerves, cross-sections are plastic-embedded and semi-thin sections are prepared.

Skeletal muscle The vastus lateralis, gastrocnemius and peroneus longus are bisected for fixation and freezing. Fixed portions are orientated in cross-section for paraffin embedding and H&E histology.

Pituitary gland and trigeminal ganglion

Half these tissues are snap-frozen, half formalin-fixed: the pituitary is sectioned in the horizontal plane, perpendicular to the stalk, with both frozen and fixed halves containing adeno- and neuro-hypophysis. Fixed portions are processed for paraffin embedding and H&E histology. At some sites, the trigeminal ganglion is bisected through its body across V2 (cut in horizontal plane into

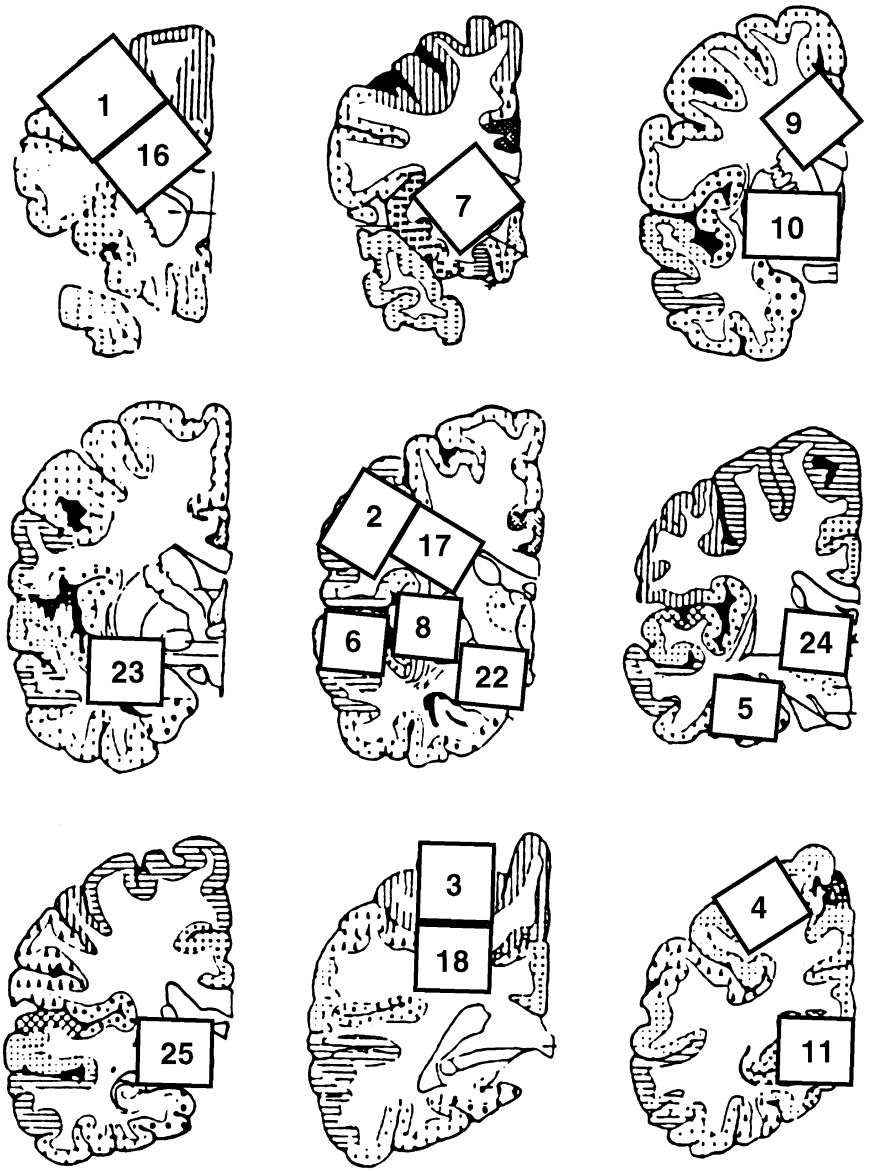

Figure 1. Hemispheric sectioning sites for the NNTC neuropathology protocol, superimposed on coronal slabs of brain oriented in the anterior/posterior commissure axis (levels 9, 10, 13, 14, 15, 18, 20, 22 and 25). Diagram courtesey of Dr. Andrew Brown and Prof. R. Perry (Andrew.Brown@nuth.northy.nhs.uk) Numbers of the blocks correspond to the verbal descriptions given in **Table 2**.

superior and inferior portions). Fixed portions are processed for paraffin embedding and H&E histology.

Dissection and storage of non-CNS tissues

One block of tissue from each organ is formalin-fixed for paraffin embedding, and the remaining tissues snap-frozen. The number of frozen portions depends on the organ. The vertebral body slice is sectioned into four portions: one for decalcification, paraffin embedding and H&E histology, the remaining three for freezing.

Removal of tissue from the bank: physical considerations

The removal and shipping of frozen tissues involves the manipulation of materials that represent an infectious risk to personnel [2]. The utilization of a small skill saw or dental drill to slice frozen tissues without thawing may

generate an aerosol, and should accordingly be done in a biologic safety cabinet or suitably contained area. This step of the entire tissue-handling setup is the most hazardous in terms of potential physical injury, breech of protective barriers and potential contamination by infectious agents, including HIV. In the USA, the shipment of tissues must conform to the US Federal Regulations 49 CFR 172 subpart H, and more universally to the UN recommendations. Transportation of frozen materials occurs on dry ice, with multiple layers of packaging to prevent leakage and appropriate labels affixed to containers. Courses to instruct bank personnel in the shipment of hazardous tissues and fluids are available commercially through organizations such as Saf-T-Pak.

Quality assurance

The NNTC recognizes that the uniform categorization of study subjects and tissue specimens is essential in creating a resource of standard quality across all participating sites. To maintain a reasonable level of diagnostic concordance among sites, quality assurance (QA) protocols have been devised in all the major disciplines involved in the study (neuropsychology, neurology, psychiatry and neuropathology). The neuropathology QA programme entails a peer review process with 'round robin' shipment of histological sections, for timely evaluation by neuropathologists representing each of the Consortium sites. The pathologists are asked to categorize histologically the specimens according to the diagnostic choice list displayed in Table 3. The diagnosis list was created by the NNTC pathology subcommittee, and is not based on prior systems for disease classification. The decision to create a novel diagnosis list was made after extensive discussion over the pros and cons of utilizing extant medical classification systems. It was felt that the most common system, SNOMED, was cumbersome and would not impart adequate flexibility and precision in the characterization of HIV-related neuropathologies, and a simple, CNS-specific system was preferred. Accordingly, utilizing the expertise of individual site pathologists, and based upon pre-extant neuropathologic literature, this novel list was created.

For the purposes of pathology QA, conference calls are to be held at quarterly intervals through the year, to discuss and attempt to resolve cases where there is significant variation in diagnosis from site to site. This peer review process will form the basis for standard diagnostic categorization and will provide continuing education to all participating neuropathologists.

Patient and specimen accrual and distribution

One of the major strengths of the Consortium is its ability to rapidly assemble a significant resource in a time of dwindling supplies. Most of the clinical studies in the Consortium began in January 1999. As of February 2001 (roughly 2 years of active study), a total of 634 persons had been followed in the NNTC, with comprehensive neurologic, psychologic and psychiatric evaluations. More than 260 CSF samples and over 450 blood samples had been collected and processed. A total of 159 brain specimens were collected, including 140 HIV-infected and 19 control cases. Thus, with regard to patient recruitment and specimen acquisition, the benefits of a consortium model were realized: in a short period of time, a substantive resource was created with abundant clinical information, patient enrolment and specimen availability.

The first request for tissue was received at the NNTC Coordination Office (NCO) in late December 1999. Within roughly half a year, a total of 19 requests were received. As a result of the rapid accumulation of samples due to the formation of the Consortium, and the coordination efforts of the NCO, the NNTC was able to deliver over 220 specimens in response to the 19 requests over a roughly half-year period. The Consortium has also shown flexibility in its tissue delivery, and has been able to supply items not standard in the NNTC protocol (for example, heart and lung specimens) for a small number of investigators. The Consortium's maximal ability to deliver specimens has not yet been approached, as knowledge of the NNTC's resources is not yet widespread. As there has been greater supply and demand, the NCO and individual banks have performed basic reviews of investigator's biographic information, funding sources, proposed studies and specimen request, evaluating the feasibility and relevance of proposed studies. A request review committee, to be composed of individual site representatives, operating under structured criteria for review, will be formulated shortly, and priority scores assigned to requests for potential future triage.

Table 3. Diagnostic categories for neuropathologic evaluation of brains, spinal cords and nerves in the NNTC

Category
Brain
1. Normal
2. Aseptic leptomeningitis (in absence of other local pathology)
3. HIV encephalitis
4. CMV encephalitis (includes ventriculoencephalitis, microglial nodule encephalitis wit. CMV inclusions, focal CMV necrosis)
5. Microglial nodule encephalitis, not otherwise specified (encephalitis without diagnostic inclusions or organisms)
6. Toxoplasmosis, active
7. Toxoplasmosis, healed
8. Cryptococcus
9. Progressive multifocal leukoencephalopathy
10. Lymphoma (primary and concurrent with systemic, meningeal and/or parenchymal)
11. Bacterial leptomeningitis
12. Bacterial parenchymal infection
13. Tuberculosis
14. Other infections
15. Anoxic-ischemic encephalopathy (focal or global)
16. Alzheimer type 2 astrocytosis
17. Focal (territorial) infarct (large or small, and due to embolism or local vascular pathology, recent or remote)
18. Hemorrhage, dura or leptomeninges (acute or organizing, due to any cause)
19. Hemorrhage, parenchymal
20. Other, non-infectious pathology
21. Minimal, non-diagnostic abnormalities
Spinal cord/nerve
22. Normal
23. HIV myelitis
24. CMV myelitis (includes myeloradiculopathy)
25. Vacuolar myelopathy
26. Microglial nodule myelitis, not otherwise specified
27. Toxoplasmosis
28. Cryptococcus
29. Aseptic leptomeningitis
30. Lymphoma
31. Bacterial leptomeningitis
32. Bacterial parenchymal infection
33. Tuberculosis
34. Other infections
35. Anoxic-ischemic damage
36. Hemorrhage, dura or leptomeninges
37. Hemorrhage, parenchymal
38. Peripheral neuropathy
39. Other, non-infectious pathology
40. Minimal, non-diagnostic abnormalities

Conclusion

The NNTC is a new enterprise that has several unique characteristics: it represents the first attempt at formalized linkage of independent human tissue banks with uniform clinical and pathological evaluation protocols; it focuses on the central and peripheral nervous system complications of HIV infection; it is capable of providing detailed clinical information attached to specimens for any qualified investigator, regardless of geographical site; it is responsive to individual member banks through their participation in the Consortium Steering Committee; and it goes beyond serving traditional non-transplant anatomic bank functions by using its resources in Consortium-initiated and individual site-initiated research. Although other multicentre brain banking research groups exist, their prime purpose has been for internally driven research, and thus the research infrastructure provided by the NNTC is, to our knowledge, unique. The Consortium has been able to generate

a large number of uniformly characterized specimens in a short period of time to fulfill tissue and fluid requests within its first year of operation. The NNTC serves as a model of cooperative tissue banking that should prove a valuable template for designing other kinds of resources serving the medical research community.

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