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Sommaire

L'Hôpital de Jour en Psychiatrie: Diversité ou Spécificité?

Day Care Hospital in Psychiatry: Diversity or Specificity?

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Abstract: Day Care Hospitals represent efficient structures for the treatment of various psychatric disorders through a large variety of medical care. In the litterature, multiple terms are used to define the various models of Day Care Hospitals, according to their use, their orientation and their therapeutic programmes. Our aim in this study is to compare, through a search on "Medline", the various existing models of Day Care Hospitals in France and in Belgium. Thereafter, the "specific" model which exists at the Centre Hospitalier du Luxembourg will be described. Two main types of Day Care Hospitals are described in the litterature: the "classical" type, with mainly a support fuction, resides on the downstream side of hospitalisation and the "specific" type, with a care function for a short duration, resides on its upstream side. The model developed at the Centre Hospitalier du Luxembourg is upstream the hospital. From our study, it is concluded that, rather of being an inconvenience, the large number of existing Day Care Hospitals, which differ by various specificities, represent excellent complementary opportunities for the current care of mental diseases.

Keywords: Day care hospital; Psychiatry; Centre Hospitalier de Luxembourg.

Résumé: Les Hôpitaux de Jour sont des structures efficaces dans le traitement de nombreux troubles psychiatriques pour lesquels ils offrent une grande diversité de soins. La variété des modèles rencontrés d'hôpitaux de jour est déterminée en fonction de leur utilisation principale. Cet article décrit ceux utilisés en Europe, et plus précisément en France, en Belgique et au Luxembourg. Les différents modèles proposés, par leur diversité ou spécificité, permettent-ils une prise en charge adaptée à la variété des pathologies rencontrées? On en trouve deux principaux dans la littérature. Le modèle «classique» ayant davantage une fonction de soutien et de réhabilitation pour des patients atteints majoritairement de psychoses chroniques. Ils sont situés en aval de l'hospitalisation. Le modèle «spécifique»

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propose une prise en charge structurée, pour une durée limitée. Les patients sont des actifs demandeurs de soins, intégrés dans des groupes selon la pathologie qu'ils présentent, c'est-à-dire en fonction de critères d'admission très stricts. Ils sont situés en amont de l'hospitalisation. L'hôpital de jour du Centre Hospitalier du Luxembourg a sa place en amont de l'hôpital. La prise en charge est spécifique, intensive et intègre la psychothérapie (cognitivo-comportementale), la pharmacothérapie et l'approche psycho-sociale. Les différents modèles décrits dans cet article ne sont pas opposables, mais au contraire permettent d'apporter une large offre de soins adaptés aux patients et aux pathologies rencontrés dans le système de santé mentale actuel.

Mots clés: Hôpital de jour; Psychiatrie; Centre Hospitalier de Luxembourg.

I/ Introduction

L'hôpital de jour psychiatrique peut être défini comme une structure fournissant des soins pendant la journée dans un cadre hospitalier [1]. Il s'agit d'une structure déjà ancienne qui propose des soins de type communautaires. Il s'est révélé efficace pour la prise en charge de nombreux troubles psychiatriques et offre une grande variété de traitements sans le coût important d'une hospitalisation à temps complet [2]. Dans la littérature, il existe de nombreux termes utilisés pour distinguer les différents modèles d'hôpital de jour. Ceux-ci sont différenciés en fonction de leur utilisation, de leur orientation et/ou de leurs programmes thérapeutiques.

Au sens le plus large, la littérature fait référence à la notion de «concept thérapeutique» d'hôpital de jour. Certains auteurs définissent l'hôpital de jour comme un plateau technique implanté au cœur de la communauté sociale ou socio-professionnelle, permettant l'approche préventive (éducation sanitaire, dépistage précoce), thérapeutique (soins intensifs par la fréquence, la multidisciplinarité et la technicité) et réadaptative des troubles de la santé mentale [3]. La terminologie anglo-saxonne est plus explicite en différenciant les «Day Treatment Center», c'est-à-dire le pôle thérapeutique, des «Day Care Center», qui met en avant le pôle psycho-social [4].

D'après Marshall [5], les hôpitaux de jour en psychiatrie auraient été introduits en Russie dans les années trente, puis aux Etats-Unis et en France. En 1947, Cameron présente une première communication sur un Hôpital de jour devant l'Association Américaine de Psychiatrie. L'hôpital de jour était destiné à traiter essentiellement des patients n'ayant jamais fait auparavant de séjour en hôpital psychiatrique. Cette approche reste actuellement une des principales dynamiques selon laquelle l'hôpital de jour fonctionne [4].

Dans les années 70, les hôpitaux de jour ont été particulièrement utilisés en tant qu'unique alternative à l'hospitalisation. La prise en charge était principalement sociothérapeutique [5]. En Belgique, le premier hôpital de jour se positionnait

davantage comme une «structure avancée» ou une alternative à l'entrée dans le champ traditionnel de la psychiatrie. Il était donc situé en amont de l'hôpital. La prise en charge était principalement psychothérapeutique en individuel et/ou en groupe [4]. Au Luxembourg, les traitements psychiatriques ont évolué depuis la théorie de l'isolement du début du 20ème siècle aux soins favorisant la réinsertion des patients [6]. En Europe, depuis les vingt dernières années, une grande variété de modèles d'hôpital de jour s'est développée avec un nombre en constante augmentation [1]. Leur rôle s'étend de l'intervention de crise suite à une consultation en urgence [7, 8] à la réhabilitation avec des soins au long cours, en passant par des centres proposant des activités journalières structurantes et des centres hautement spécialisés dans des programmes psychothérapeutiques.

De nos jours, la psychiatrie subit de nombreux changements qui interviennent à différents niveaux et impliquent directement les hôpitaux de jour. Ces changements soulèvent de nombreuses questions: au niveau du parcours de soin, l'hôpital de jour doit-il être en aval de l'hospitalisation temps plein avec comme objectif de réduire la durée des hospitalisations et de mieux assurer le suivi, ou en amont afin d'éviter et prévenir les hospitalisations, ou bien doit-il être les deux à la fois? L'infrastructure la plus adaptée doit-elle poursuivre de nombreux projets mais peu spécifiques, être centrée sur un nombre limité de projets très spécifiques, ou bien alors être les deux à la fois? Le mode de fonctionnement le mieux adapté doit-il être de huit heures par jour ou des demi- journées discontinues dans la semaine? Les durées de prise en charge doivent-elle être déterminées préalablement ou non? Enfin, doit-il s'agir d'une population non sélectionnée ou bien spécifique répartie selon le diagnostic?

Le but de cette étude est de faire une revue de la littérature, de décrire les différents modèles existants d'hôpitaux de jour et de préciser leurs caractéristiques et leurs types de prises en charge. Dans une première partie, nous verrons différents modèles rencontrés en Europe et plus particulièrement en France et en Belgique, puis nous présenterons le modèle d'hôpital de jour développé au Centre Hospitalier du Luxembourg. Enfin, nous discuterons de l'intérêt de la diversité et de la spécificité des hôpitaux de jour.

II/ Une grande diversité de modèles

Nous avons réalisé une recherche par «Medline» d'études publiées avec les termes «day hospital», «partial hospitalization», «day center treatment» et «day center care».

A/ En France, il existe deux alternatives à l'hospitalisation complète. Ce sont les hôpitaux de jour et les Centres d'Accueil Thérapeutique à Temps Partiel (CATTP) [9].

Les hôpitaux de jour assurent des soins polyvalents, individualisés, intensifs, prodigués dans la journée, dans le but d'optimiser l'insertion des personnes dans leur

milieu familial ou professionnel à travers des actions psychologiques, sociologiques, thérapeutiques, éducatives et d'accompagnement. C'est une seule et même équipe qui prend en charge le patient. Des différences dans les hôpitaux de jour pour adulte existent entre les structures sectorisées et celles non sectorisées [9]. Dans les hôpitaux de jour sectorisés, le personnel infirmier est présent en plus grand nombre. Les consultations psychiatriques hebdomadaires et les thérapies institutionnelles sont plus fréquentes. Les psychoses représentent les pathologies principales des patients. Dans les hôpitaux de jour non sectorisés, le personnel participant aux soins est plus diversifié. Les troubles de l'humeur et les troubles névrotiques sont plus fréquents que les psychoses. Les patients sont plus jeunes et ont des pathologies plus diverses. La prise en charge est continue dans la semaine et plus intensive [9]. Les consultations psychiatriques sont plus fréquentes hors de la structure, notamment dans les Centres Médico-Psychologiques (CMP). Ces hôpitaux de jour offrent la possibilité d'un hébergement associé, sanitaire ou médico-social. Ils favorisent très fréquemment la réalisation d'une activité professionnelle extra-institutionnelle. Dans les hôpitaux de jours non sectorisés pour enfants, les séances de psychomotricité, d'orthophonie et de psychothérapie individuelles sont plus fréquentes que dans les sectorisés.

Les CATTP sont des structures qui visent à maintenir ou à favoriser une existence autonome par des actions de soutien et de thérapie de groupe, avec une prise en charge plus ponctuelle, offrant à des petits groupes de patients différentes activités dans un cadre déterminé et régulier [10]. Le mode de fonctionnement est plus discontinu. La capacité d'accueil est plus réduite. Les patients souffrant de troubles de l'humeur et de troubles névrotiques sont également plus fréquents que les patients souffrant de troubles psychotiques [9].

B/ En Belgique, il existe des hôpitaux de jour de natures très différentes. Certains de ces hôpitaux de jour sont issus de macro-institutions rassemblant un grand nombre de pavillons. Ils sont habituellement situés au sein même d'un hôpital psychiatrique. D'autres hôpitaux de jour sont issus de micro-institutions indépendantes, c'est-à-dire ne faisant pas partie d'un grand groupe organisé et n'ont pas de lien architectural avec un hôpital. Ils sont réservés habituellement à des patients ayant une pathologie bien spécifique (psychoses infantiles, toxicomanies) [4]. J. Bertrand apporte une vision assez spécifique de l'hôpital de jour. Pour être admis, le patient doit être un actif demandeur de soins et être capable de définir avec l'équipe pluridisciplinaire un contrat thérapeutique à partir du motif d'entrée. Ce contrat doit aussi permettre de renforcer positivement la motivation ou contribuer à la clarifier. La majorité des méthodes thérapeutiques utilisées dans les services d'hospitalisation de psychiatrie, et plus spécifiquement les méthodes de groupes, les activités communautaires et les techniques de communication interpersonnelle, peuvent également s'appliquer en hôpital de jour. Les hôpitaux de jour font appel à des orientations psychothérapeutiques diverses, avec cependant habituellement une certaine prédilection pour une orientation précise variable se-

lon les hôpitaux. L'hôpital de jour doit être par conséquent une unité thérapeutique de soins intensifs variés, avec une complémentarité indispensable avec les autres structures de soins de santé mentale. Les évolutions les plus favorables observées sont celles où les patients se dégagent rapidement de la prise en charge intensive, sans pour autant couper le contact. L'hôpital de jour ne doit en aucun cas être considéré comme une structure rivale de l'hôpital psychiatrique, mais en être une structure complémentaire avec des champs qui se recouvrent et se complètent [11]. Actuellement, son image s'est dédramatisée et les progrès thérapeutiques rapportés sont mieux reconnus. Enfin, l'hôpital de jour offre d'autres avantages. Le malade est un actif demandeur de soins qui se rend tous les jours à l'hôpital à horaire fixe. Cela permet ainsi d'éviter la séparation avec le milieu familial et donc permettre de le confronter aux problèmes courants. L'hôpital de jour est aussi un lieu privilégié d'observation pour affiner un diagnostic et contrôler la prise médicamenteuse [12].

C/ De nombreux auteurs d'autres pays d'Europe définissent actuellement le plus souvent l'hôpital de jour en fonction de son utilisation principale et de sa place dans le système de soins en santé mentale. D'une façon générale, les auteurs différencient quatre types de soins journaliers qui ont prouvé leur efficacité thérapeutique sur des essais contrôlés randomisés.

Le premier type de soins privilégie la surveillance, le soutien et la réhabilitation des patients souffrant de pathologies chroniques, principalement de psychoses de type schizophrénique [1, 13, 14]. Pour ces pathologies, l'utilisation de l'hôpital de jour, a prouvé une efficacité supérieure aux traitements en ambulatoire. Ce type d'hôpital peut également être considéré comme une structure de soins journaliers de type occupationnel, où se rendent les patients atteints de pathologies chroniques [13]. Il est le plus souvent localisé dans l'institution psychiatrique à laquelle il est rattaché ou bien à proche distance. Il offre très souvent la possibilité d'être logé jusqu'au lendemain L'équipe est composée d'une faible proportion de professionnels médicaux. Etant donné que plus d'un tiers des patients présentent une psychose, l'orientation pharmacologique est prépondérante. En revanche, la psychothérapie est le traitement le moins investigué. Pour cette population de patients, les critères de sélection ne doivent pas être trop rigoureux et la durée de traitement doit être peu limitée. Les patients sont en moyenne plus âgés, ont un niveau d'éducation plus bas, et sont principalement référés par les services d'hospitalisation. Ce type d'hôpital de jour fonctionne avec un coût relativement bas. Les hôpitaux de jour ayant une orientation plus sociothérapeutique ont en commun la localisation dans l'enceinte de l'hôpital et la longue durée du séjour. En revanche, ils ont moins de places et proposent plus fréquemment un travail en individuel [1]. Lorsqu'il s'agit de thérapie occupationnelle utilisée principalement dans les hôpitaux de réhabilitation chez les patients psychotiques, l'équipe travaille moins fréquemment à temps complet.

Le deuxième type de soins constitue plutôt une alternative à l'hospitalisation en cas de décompensation aigüe ou sub-aigüe [1, 13, 14]. Pour ces cas, l'hôpital de jour est le plus souvent localisé dans l'institution psychiatrique à laquelle il est attaché ou bien il est situé à très proche distance. L'équipe est majoritairement médicale, et près d'un tiers des patients provient de la consultation de psychiatrie. La durée du traitement est courte, et il existe une possibilité d'être logé jusqu'au lendemain, ce qui est un facteur essentiel pour éviter une hospitalisation à temps complet. En revanche, il n'y a pas de caractéristiques spécifiques concernant les pathologies, les procédures de sélection et l'âge des patients.

Le troisième type de soins est une transition entre l'hospitalisation complète et le retour définitif au domicile, permettant ainsi de raccourcir la durée de cette hospitalisation [1, 14]. Pour certains auteurs, cette transition est définie davantage comme une forme de continuité à l'hospitalisation complète. Ces hôpitaux de jour ont des caractéristiques communes avec ceux donnant le premier type de soin.

Le quatrième type de soins est représenté par l'alternative intensive aux soins thérapeutiques proposés en ambulatoire [1, 14]. Dans ce cas, il s'agit d'hôpitaux de jour qui admettent des patients suite à un traitement ambulatoire ne produisant pas les résultats attendus ou se prolongeant, mais qui ne justifie pas une hospitalisation. Ils sont le plus souvent localisés à une certaine distance de l'institution psychiatrique. L'équipe est en grande partie constituée de psychologues. Les diagnostics principaux sont les troubles névrotiques, les troubles de la personnalité ou les états dépressifs, et les critères de sélection sont stricts. Les patients sont en moyenne plus jeunes, ont un niveau d'éducation plus élevé et proviennent dans plus de la moitié des cas des centres de consultation. L'approche psychothérapeutique réalisée majoritairement par des psychologues est intensive, de longue durée et les thérapies se font souvent en groupe [14].

Pour d'autres auteurs, il n'existe pas de véritables différences de profils entre les hôpitaux de jour, c'est-à-dire que chacun est susceptible de fournir une grande diversité de fonctions et de prise en charge quelles que soient les pathologies rencontrées [15].

III/ Le modèle développé au Centre Hospitalier de Luxembourg

L'hôpital de jour du Centre hospitalier du Luxembourg [16] est un hôpital de jour psychiatrique pour adultes fonctionnant de huit heures à dix sept heures, du lundi au vendredi. Il est situé en dehors de l'hôpital, mais dans l'enceinte du Centre Hospitalier. La prise en charge des patients, active et intensive, intègre psychothérapie (cognitivo-comportementale), pharmacothérapie et approche psycho-sociale. Il s'agit avant tout de traitements ciblés, pour des troubles spécifiés, dont la durée est limitée dans le temps et proposés sous la forme de thérapies de groupe, selon des programmes spécifiques, élaborés à l'avance.

L'hôpital de jour du Centre Hospitalier de Luxembourg a sa place en amont de l'hôpital. Il a pour objectifs essentiels d'éviter les hospitalisations, la psychiatrisation, la stigmatisation, les complications, la survenue d'autres troubles ou l'évolution vers la chronicité. Il doit permettre de transposer les apprentissages faits dans le milieu thérapeutique vers l'environnement habituel, de maintenir une insertion familiale, professionnelle et sociale existante et de remédier aux intégrations déficientes. Les méthodes psychothérapeutiques de groupes utilisés sont de type cognitivo-comportemental. Elles sont accompagnées parallèlement, en cas de besoin, d'un traitement psychothérapeutique individuel, d'un traitement médicamenteux ou d'un accompagnement psycho-social. Les programmes thérapeutiques font appel à des techniques cognitivo-comportementales telles que la restructuration cognitive, les méthodes de confrontation et d'exposition, la résolution de conflits, les jeux de rôles ou l'affirmation de soi. Le patient participe activement à l'apprentissage de techniques de communication, de développement des habilités sociales, de gestion du stress et des émotions, du contrôle des tendances impulsives, de méthodes de relaxation et de contrôle de la respiration. Chaque groupe est dirigé par un thérapeute (et parfois un co-thérapeute). Chaque groupe est constitué de six à huit patients présentant un trouble identique ou ayant des difficultés similaires. De multiples évaluations sont réalisées afin de préciser le diagnostic et la gravité du trouble. Les évaluations sont aussi utilisées pour évaluer le changement obtenu par le traitement et pour estimer l'intérêt d'un programme thérapeutique afin de l'adapter et de le perfectionner en fonction des résultats obtenus. L'équipe est constituée d'un psychiatre, de trois psychologues-psychothérapeutes, d'un psychologue psychomotricien, de deux infirmières psychiatriques, d'une assistante sociale et d'une secrétaire.

L'hôpital de jour prend actuellement en charge de façon spécifique les troubles suivants, selon des programmes bien définis:

Le Trouble panique et l'Agoraphobie. Le programme comprend une psycho-éducation relative au trouble panique et aux mécanismes qui le sous-tendent (par exemple l'hyperventilation), un apprentissage du contrôle respiratoire, une analyse du contexte de vie dans lequel se sont développées les attaques de panique, un apprentissage des techniques de relaxation et de la gestion des attaques de panique, une analyse et une restructuration cognitive des pensées dysfonctionnelles, des expositions aux sensations intéroceptives et des expositions in vivo aux situations redoutées. Le programme comprend huit séances hebdomadaires de deux heures.

Le Trouble Anxieux Généralisé (TAG). Le programme comprend une psycho-éducation relative au TAG, une analyse et un travail de restructuration des soucis, un apprentissage des techniques de contrôle rapide de l'anxiété et du contrôle respiratoire, un apprentissage des techniques de relaxation, une restructuration cognitive des pensées négatives et une identification des distorsions cognitives, un travail de restructuration des croyances, un apprentissage des techniques de

résolution des problèmes, une désensibilisation aux situations stressantes et une prévention du retour des soucis. Le programme comprend quinze séances hebdomadaires de deux heures.

La boulimie. Le programme comprend une psychoéducation relative à la boulimie, une analyse du comportement alimentaire et une discussion des motivations personnelles amenant la personne à vouloir changer ce comportement. Il a pour buts de fixer des objectifs réalistes, d'assouplir les interdits alimentaires, de développer des stratégies de contrôle des crises boulimiques et de favoriser l'apprentissage de la gestion des émotions. Il comprend des séances de relaxation et un travail relatif à l'affirmation de soi, à l'estime de soi, à l'image du corps, et au développement des relations sociales et familiales. Il est complété par des séances consacrées à l'organisation d'un programme d'activité physique, à un travail sur les pensées négatives, et à un apprentissage des techniques de résolution de problèmes. Le programme comprend vingt séances hebdomadaires de deux heures.

La dépression. Le programme est destiné au traitement des dépressions majeures non psychotiques, non bipolaires, chroniques ou récidivantes. Il comprend une psycho-éducation relative aux troubles dépressifs, un travail sur les émotions, un travail sur le deuil ou sur d'autres pertes, une analyse des conflits interpersonnels, une mise en évidence des pensées négatives automatiques, une restructuration des pensées dysfonctionnelles, un apprentissage des techniques d'affirmation de soi, de communication et de résolution des conflits et enfin un travail sur la prévention des rechutes. Le programme comprend dix séances hebdomadaires de deux heures.

L'hyperphagie boulimique (binge eating disorder) et le surpoids. Le programme commence par une psychoéducation relative à l'hyperphagie et au surpoids. Il a comme objectif de faciliter le changement du comportement alimentaire en vue d'un amaigrissement. Il comprend une analyse du comportement alimentaire, la fixation d'objectifs réalistes, la définition de la motivation personnelle, la redécouverte des sensations corporelles, la gestion des émotions, un apprentissage de la relaxation de Jacobson et des techniques d'affirmation de soi. Il permet aussi un travail sur l'estime de soi, sur l'image du corps, sur les pensées négatives et sur le développement des relations sociales. Il propose des activités sportives douces et progressives, ainsi qu'un apprentissage des techniques de résolution de problèmes. Le programme comprend quinze séances hebdomadaires de deux heures.

La phobie sociale. Le programme a pour objectif de développer les capacités d'affirmation de soi. Il commence par une psychoéducation relative à l'anxiété sociale, une auto-observation des situations sociales qui posent problème, un apprentissage de la relaxation de Jacobson, une analyse et une utilisation du non-verbal. Il est complété par un travail sur les pensées négatives et sur le développement de l'estime de soi, un apprentissage des techniques d'affirmation de soi, et des

expositions graduées aux situations sociales redoutées. Le programme comprend quinze séances hebdomadaires de deux heures.

Les troubles de l'adaptation avec humeur dépressive et/ou anxieuse. Le programme comprend un apprentissage de la relaxation musculaire progressive de type Jacobson, des techniques du contrôle respiratoire et d'affirmation de soi, un travail sur les pensées négatives et une restructuration cognitive de ces pensées. Il comprend des discussions en groupe, des jeux de rôle, et l'apprentissage d'une meilleure gestion des situations difficiles rencontrées par chaque participant. Le programme comprend quinze séances hebdomadaires de deux heures.

Le Trouble Obsessionnel-Compulsif (TOC). L'objectif de ce programme est d'aider les patients à mieux gérer leurs obsessions et leurs compulsions. Il comprend une psychoéducation relative au trouble, une mise en évidence des pensées dysfonctionnelles, une remise en question du système de croyance erroné, et une élaboration de pensées alternatives. Il accorde une importance particulière à la technique de l'exposition avec prévention de la réponse, qui consiste à encourager le patient à s'exposer à chacune des situations qui lui font peur tout en s'abstenant d'y répondre par des compulsions, des rituels ou la recherche de réassurances. Le programme comprend quinze séances hebdomadaires de deux heures.

Le stress. Il s'agit d'un programme de gestion du stress ayant pour objectif le développement des capacités personnelles d'adaptation au stress. Il est destiné à des personnes ayant des difficultés professionnelles engendrant un stress et présentant habituellement un comportement de type A (vie très active). Ces personnes présentent souvent une anxiété de performance, ont fréquemment des difficultés relationnelles avec leur entourage, ou encore éprouvent des difficultés suite à un changement de vie ou de milieu. Le programme comprend une psycho-éducation concernant le stress, un apprentissage des différentes techniques de relaxation et de résolution de problèmes, un travail sur les capacités de communication, ainsi qu'une analyse cognitive et une restructuration des pensées dysfonctionnelles. Il est complété par un apprentissage des techniques de gestion du temps, de planification des activités quotidiennes et de gestion des émotions, une réflexion sur l'importance d'une bonne hygiène de vie et une définition personnelle des priorités. Le programme comprend dix séances hebdomadaires de deux heures.

Le manque d'estime de soi. Ce programme concerne les personnes manquant de confiance en eux-mêmes. Le manque de confiance en soi peut être en rapport avec une situation familiale ou professionnelle difficile, par exemple la perte d'un emploi ou un divorce. Ailleurs, il a pu s'installer suite à un épisode de maladie ou à un handicap physique ou psychique survenu après un accident ou une maladie. Le programme concerne également les personnes ayant un sentiment d'infériorité par rapport aux autres, ou ayant des doutes sur leurs capacités ou leur valeur personnelle. Il comprend un apprentissage des techniques de contrôle respiratoire et de relaxation, un travail sur l'imagerie mentale, la connaissance de soi et la

gestion des pensées négatives. Il a pour but de développer des perceptions et des pensées positives, d'aider les participants à expérimenter de nouvelles façons d'être, à accepter l'échec, à savoir se ressourcer et à prendre soin d'eux-mêmes. Le programme comprend seize séances hebdomadaires de deux heures.

Le manque de compétences sociales. Il s'agit d'un programme d'entraînement aux habilités sociales destiné à des personnes qui ont des difficultés à établir des relations avec autrui, qui ont du mal à exprimer leurs difficultés ou à se détendre en société, ou qui expriment leurs émotions sur un mode passif ou agressif. Il s'adresse aussi aux personnes qui présentent une timidité excessive, à celles qui ont des difficultés à exprimer une demande ou un refus ou qui ont tendance à se laisser exploiter par les autres. Le programme comprend des exercices de relaxation, des techniques respiratoires, un apprentissage du choix des mots, de la tonalité de la voix et des expressions adaptées à certaines situations. Il comprend aussi des exercices pour apprendre à observer le non verbal dans une discussion, à identifier les sentiments et les souhaits de l'interlocuteur. Le programme comprend vingt séances hebdomadaires de deux heures.

La tension nerveuse. Il s'agit d'un programme comprenant essentiellement des séances de relaxation, d'apprentissage du contrôle respiratoire, et de sophrologie. Il est destiné à des personnes présentant une anxiété, une tension nerveuse, des tendances dépressives, un surmenage, une insomnie ou une asthénie, des céphalées de tension, des douleurs mal définies ou une hypertension artérielle. Il comprend l'apprentissage de la relaxation de Jacobson avec ses versions, courte ou longue, ainsi que l'apprentissage de différentes techniques de respiration, le recours à une image de détente, ainsi qu'un feed-back des exercices effectués. Chaque participant reçoit une cassette comprenant des exercices de relaxation à faire à domicile. Le programme comprend six séances hebdomadaires de deux heures.

IV/ Discussion

La classification des hôpitaux de jour en fonction de leur utilisation principale détermine en partie leurs caractéristiques, les pathologies rencontrées, le type de prise en charge, leur localisation de l'hôpital de jour, la composition de l'équipe, l'origine des patients et la durée du traitement.

Selon B. Kabuth [17], la spécialisation des hôpitaux de jour soulève néanmoins un certain nombre de questions: il s'agit avant tout d'un phénomène inévitable ayant conduit à l'ouverture d'unités de plus en plus spécialisées dans la prise en charge d'un trouble spécifique. Aux Etats-Unis, les durées de séjour se négocient quasiment au jour le jour, avec des suivis en ambulatoire toujours limités dans le temps. Il existe de nombreuses «cliniques» qui sont réparties par symptômes ou groupes symptomatiques. Ce système très pragmatique permet d'offrir une réponse médicale rapide, de créer une grande alliance thérapeutique avec les patients, et de présenter une efficacité incontestable dans le domaine de la recherche (groupe

homogène de patients, thérapies limitées dans le temps). Il permet l'acquisition par les équipes d'un savoir faire clinique et l'apport de connaissances nouvelles et pointues. Cela facilite considérablement l'évaluation des pratiques. Néanmoins, ce système comprend les risques suivants. Une prise en charge des patients par surspécialité, l'accumulation des co-morbidités, des thérapies et des médications. Cela incite à une prise en charge axée sur le symptôme et de considérer le sujet uniquement comme objet de science. La spécialisation semble représenter l'avenir de l'hôpital de jour, mais elle doit se préserver des dérives par l'apport essentiel de la «psychothérapie institutionnelle», c'est-à-dire des réunions de synthèse indispensables et de la supervision psychanalytique des équipes.

V/ Conclusion

La revue de la littérature a permis de mettre en évidence deux types de modèles d'hôpital de jour. Le modèle «classique» fait référence à des hôpitaux de jour ayant avant tout une fonction de prise en charge, de réhabilitation et de soutien pour les patients atteints majoritairement de psychoses chroniques. Il s'agit le plus souvent de structures accueillant les patients pour la journée, selon des critères d'admission qui ne sont pas sélectifs et avec de longues durées de séjour. Ces hôpitaux de jour accueillent majoritairement les patients après une ou plusieurs hospitalisations, et sont situés en aval de l'hospitalisation. Le modèle «spécifique» d'hôpital de jour concerne une structure dynamique, où le patient est un actif demandeur de soins, avec une prise en charge structurée et encadrée pour une durée limitée dans le temps. Les patients sont admis dans des groupes en fonction de la pathologie qu'ils présentent, c'est-à-dire en fonction de critères d'admission très sélectifs. Il s'agit d'une prise en charge complémentaire au traitement en ambulatoire, et située en amont de l'hospitalisation. L'orientation est principalement psychothérapeutique. Cette diversité ou spécificité dans la prise en charge de chacun ne doit en aucun cas être opposée, mais être considérée comme complémentaire afin d'apporter une large offre de soins dans le système de santé mentale actuel. La recherche dans le domaine des hôpitaux de jour devrait permettre de mieux définir les concepts thérapeutiques d'hôpital de jour afin de comparer les structures selon une méthodologie adéquate pour élaborer des recommandations.

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Intramuscular olanzapine in patients with schizophrenia: an observational study in an emergency room

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Abstract:

BACKGROUND Between 2001 and 2005 important changes were observed in expert opinion about the clinical management of patients with schizophrenia (SCZ) and agitation requiring an IM psychotropic, with a growing interest for IM atypical antipsychotics. STUDY OBJECTIVES In an effort to acquire a typical, medically and psychiatrically unselected population of severely agitated patients with SCZ, we conducted a naturalistic study in an emergency setting, consecutively enrolling agitated patients who refused oral treatment. METHOD Measures were collected prospectively for patients with acute agitation and schizophrenia (DSM IV diagnosis criteria) who consulted consecutively two ED: one in Belgium and the other one in Switzerland. Consent was obtained subsequently. A group of 40 patients with severe agitation and SCZ received olanzapine 10 mg IM. Efficacy and safety data (blood pressure, pulse, extrapyramidal symptoms) were assessed at baseline, two hours post-injection and at discharge. RESULTS Significant reductions of agitation associated with good tolerance were observed two hours after the first IM olanzapine (PANSS EC declined from 28.6 ± 4.13 to 16.8 ± 4.8). Only 5% of patients required a second IM olanzapine. The absence of clinically significant extrapyramidal and cardiovascular side effects is promising, but considering the statistically significant reduction of systolic and diastolic blood pressure and pulse, vital signs should be checked especially in the first 2 hours post injection. CONCLUSIONS This naturalistic study suggest a promising efficacy and safety balance of intramuscular olanzapine in patients with acute agitation and schizophrenia in emergency.

Key words: schizophrenia, agitation, olanzapine, intramuscular, emergency.

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Location of work: Service d'urgences psychiatriques, Centre Hospitalier Régional «La Citadelle». Boulevard du Douzième de Ligne, 1. 4000 Liège, Belgique.

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Introduction

Management of psychomotor agitation raises nosological, diagnostic, legal, ethical and even logistical questions for an emergency department [1]. Historically, little attention was paid to diagnosis in the management of agitation as few choices were available. There are now more alternatives, but little data concerning the newer intramuscular (IM) psychotropics in patients with severe agitation in emergency settings [1, 2].

Between 2001 and 2005 important changes were observed in expert opinion about the clinical management of patients with agitation requiring IM psychotropic. For a patient with a provisional diagnosis of schizophrenia in 2001, expert consensus favored a combination of a benzodiazepine plus a high-potency conventional antipsychotic first line, with a conventional antipsychotic alone a high second-line option [3]. By December 2005, for the same indication, first line choices were: olanzapine (OLZ) alone, or a benzodiazepine and haloperidol, ziprasidone alone, or a benzodiazepine and ziprasidone [1]. This change could be related to recent data from randomized studies about the efficacy and the safety of atypical antipsychotics in patients with agitation and SCZ. However, in spite of several randomized studies on that topic, no consensus emerged on treatment of choice. Questions have been raised about the generalizability of randomized controlled trials with selected mildly to moderately agitated subjects to unselected populations with true emergencies [4]. More severely ill patients may be less responsive to the therapeutic effects and more susceptible to side effects [5, 6]. A number of authors have called for studies in more relevant populations [7].

In an effort to acquire a more typical, medically and psychiatrically unselected population of severely agitated patients, we conducted a naturalistic study in an emergency setting consecutively enrolling agitated patients with schizophrenia who refused oral treatment. Because this is an observational study, with no alteration of treatment, informed consent was obtained after the resolution of the

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agitation allowing for the inclusion of the most psychiatrically ill and medically ambiguous [8].

Olanzapine was used because it is the only second generation antipsychotic available for intramuscular injection in Belgium and in Switzerland. Although there are four randomized placebo and comparator controlled, double-blind clinical trials demonstrating the efficacy of OLZ in reducing acute agitation in approximately 1050 patients with schizophrenia, schizoaffective and bipolar disorder, there is no data concerning patients requiring restraint or seclusion. Several studies have provided data suggesting excellent tolerability with regard to extrapyramidal side effects [2, 9-11] and ECG perturbations [12]. However, little information is available concerning hypotension. Published results from the sponsor are underpowered to detect a difference [10]. The European Medicines Evaluation Agency reports a greater incidence of postural hypotension among patients given olanzapine (11.9%) versus with haloperidol (about 3.1%). Hypotension seems to be more frequent especially if there is an association OLZ with benzodiazepine [13].

Materials & Methods

A prospective, multicenter observational study of the safety and efficacy of IM psychotropic medication in patients with acute agitation was conducted in the ED of two hospitals: one regional hospital from Belgium and one universitary hospital from Switzerland.

Consistent with local clinical policy, all agitated patients with known or suspected schizophrenia who refused oral medication received 10 mg IM OLZ monotherapy. The decision to administer an IM injection was made by one of the regular staff, independent of the investigators. The exclusion criteria were alcohol and drug abuse or dependence, pregnancy, unstable diabetes or known intolerance to OLZ. The patients suspected of contraindications for OLZ received haloperidol alone or with promethazine in Switzerland, and droperidol in Belgium, following different local clinical policies. A second IM administration was allowed at least 2 hours after the first IM. As there was no alteration of patient care, the local ethics committee agreed that consent to use the data could be obtained after resolution of the PMA. The number of the patients in Geneva was limited to 12 by the Ethical Committee of the University of Geneva, Switzerland. The site in Belgium was not similarly encumbered and enrolled 30 patients. Two patients withheld consent to yield the sample of 40.

Consecutive patients with SCZ were treated. Diagnosis was established for some patients in prior contacts with the mental health system and for others was ascertained after the episode using the Structured Clinical Interview for DSM IV. Patients with known substance use, schizophreniform, schizoaffective disorder and bipolar disorder were excluded. An investigator not involved with the direct care of the patient assessed patients for the level of agitation and for side effects.

Agitation was assessed at entry, two hours after the first 10 mg OLZ IM administration and 12-24 hours after the first injection. Measures included PANSS-EC (Positive and Negative Syndrome Scale Excited Component: tension, uncooperativeness, hostility, poor impulse control, and excitement), ABS (Agitated Behavior Scale) and CGI-S (Clinical Global Impression-Severity). Vital signs and adverse effects were assessed at the same intervals. Movement disorders were assessed using the BAS (Barnes Akathisia Global Score) and SAS (Simpson-Angus Extrapyramidal Effects Scale).

Student's t-test assuming equal variances was used to compare changes in the PANSS-EC, ABS, CGI-S, blood pressures and cardiac frequency from baseline to 2 hours after the IM and at the discharge.

Results

The study population was comprised of 23 females and 17 males (10 patients included in Switzerland and 30 in Belgium). The mean age was 38.4 ± 13.3. Due to the severity of the agitation, physical restraint was required in 28 (70%) patients. Two patients (5%) required a second 5mg OLZ IM, 2 hours following the first IM, and one patient requiring a third 5 mg OLZ IM after the first 12 hours.

There were statistically significant reductions in PANSS-EC, ABS and CGI scores 2 hours after the first IM. The mean baseline PANSS-EC score was 28.6 ± 4.13, which declined at two hours after the first 10 mg OLZ IM to 16.8 ± 4.8 ($p<0.0001$) and at discharge to 12.1 ± 4.6 ($p<0.0001$). The reduction of the ABS scores was similar: from 36.7 ± 6.2 at entry to 21.2 ± 4.1 at two hours after the first IM ($p<0.0001$) and at discharge to 17.8 ± 5.2 ($p<0.0001$). The CGI declined from 5.9 ± 0.8 at entry to 3.4 ± 0.7 two hours after the first IM ($p<0.0001$) and at discharge to 2.8 ± 1.1 ($p<0.0001$). There were no significant differences in the initial PANSS and ABS scores or in the PANSS and ABS reductions by gender (test t-Student).

There was a mean reduction of blood pressure (systolic / diastolic, mmHg) from 134.7 ± 12.9 / 95.3± 7.4 at entry to 123.6 ± 11.8/ 87 ± 5.2 two hours after the first IM and to 122.5 ± 7.8 / 89.5 ± 3.7 at discharge. The pulse rate diminished also from 98.0 ± 9.5 at entry to 87.2 ± 7.3 two hours after the first IM and to 78.3 ± 5.7 at discharge. The mean reduction of systolic and diastolic blood pressure and beats per minute pulse at 2 hours is statistically significant (systolic, $p<0.005$; diastolic, $p<0.005$; pulse, $p<0.005$).

There were no complaints of dizziness reported spontaneously or on enquiry. Although asymptomatic, 8 patients experienced a 20 mm Hg reduction of systolic and 8 experienced a 10 mm Hg drop in diastolic blood pressure 2 hours post injection.

There was no statistically significant increase in SAS and BAS scores.

Discussion

This prospective observational study suggests good effectiveness (efficacy with few side effects) of monotherapy with 10 mg IM OLZ in patients with SCZ and acute agitation in an ED. These findings are consistent with the data from randomized studies [5, 11] and with a study of several SGA's in a heterogeneous population in an emergency setting [14].

The mean age of the patients included in the present study resembles that from the published clinical trials in the schizophrenia group assigned 10 mg IM olanzapine: 36.7 ± 12.1 years in randomized studies [11] and 36.5 ± 12 years in an open label study [14].

Randomized clinical trials of IM OLZ have included mild to moderately agitated patients with a mean PANSS-EC score between 18–19 in schizophrenia patients [9, 11, 15], contrary to the only open label in ED, were patients had an intake PANSS-EC score of 26.5 [14]. The clinical interest of naturalistic data that concern more severely ill patients than those included in randomized trials has been discussed previously [8]. This is the first observational study of olanzapine with consecutive recruitment and treatment prior to consent for patients with schizophrenia.

The significant reductions in agitation observed in this study two hours after monotherapy with 10 mg IM of OLZ are larger than those reported for consented patients with schizophrenia or bipolar disorders in other clinical trials: PANSS-EC change –11.8 here, ranging from -7 to -9.4 in randomized studies [10, 11, 15] or -9.6 in an open label study [14]. This may be related to higher entry scores, eg, the entry PANSS EC of 28.6 in this study versus 18.5 in randomized placebo controlled studies [10, 11, 15]. However, this may also be related to the lack of a placebo control. Interestingly, San et al, 2006 describe a group of patients with schizophrenia or mania and comparable baseline scores also treated with OLZ in an ED with similar reductions at 2 hours.

The rate of 5% of patients requiring a second injection is lower here than in randomized controlled trials: olanzapine, 15%, haloperidol (15%) and placebo (39%) [2], but similar to the other available open label study of bipolar and patients with schizophrenia (4.3%) [14]. The only explanation that San et al. 2006, propose for their low percentage of patient requiring a second injection is that their naturalistic study was performed in psychiatry emergency units, where nursing staff were specifically trained in the management of disturbed or violent behavior and where a psychiatrist was available at all times, conditions also similar in our study.

The safety data here are similar to that reported by the manufacturer to European and American regulators. Recently, the manufacturer has also presented data on spontaneously reported adverse events for approximately 278600 exposures in the first year post-marketing [16]. Of the 850 total olanzapine-treated individuals

in the IM olanzapine clinical trials in normal volunteers, non-agitated patients, and agitated patients, 64 individuals experienced bradycardia [17]. Twenty-eight (43.8%) of the 64 were normal volunteers and Forty (62.5%) of the 64 cases of bradycardia were associated with a decrement in resting blood pressure or an orthostatic drop. These effects and differences between treatments effectively disappeared by 24 hours following initiation of IM treatment. It would appear from clinical data collected in these trials that the state of agitation is protective against the hemodynamic effects of α1-antagonism [17].

The absence of clinically significant extrapyramidal and cardiovascular side effects in this naturalistic study is promising, but considering the statistically significant reduction of systolic and diastolic blood pressure and pulse, vital signs should be checked especially in the first 2 hours post injection and combinations with benzodiazepines are not recommended [1].

The strength of this study is that it included all available patients prior to consent and diagnosis. Data was later excluded if subjects withheld consent. This should result in a more representative and generalizable sample. Placebo response in similar studies has been low [15]. Nevertheless the lack of a control group is a limitation: the effects of antipsychotics appeared twice as large in studies with an active control as in studies with a placebo control group [18]. Although the 5 item PANSS EC is commonly used, principal components analysis has found that the tension item is not highly correlated with the other items in this scale [19]. Finally, additional safety data in a relatively unselected population is also needed. We estimate that that approximately 100 olanzapine subjects and 100 placebo subjects would be required to detect a statistically significant difference in hypotension [10]. Those data are comparables with some other studies focusing on patients with borderline personality disorders and agitation in emergency [20, 21]. Because of the smaller sample size, the findings here should be interpreted cautiously.

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Brain repair
how stem cells are changing neurology

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Abstract:

The concept that everything can die, but nothing can regenerate in the brain has been replaced with new hope that stem cells will provide avenues to repair the damaged central nervous system (CNS). The treatment of brain damage has been demonstrated preclinically using a variety of stem cell sources. The prototypical cell that gives rise to the CNS is the neural stem cell (NSC). NSCs differentiate into site-appropriate phenotypes when transplanted into the damage brain and can recover lost functions. In some cases, cells can be pre-differentiated into a particular neuronal phenotype, such as dopaminergic cells, that can then be transplanted ectopically to promote behavioural improvements in conditions like Parkinson's disease. Early clinical studies in PD have demonstrated the proof of principle that this approach can improve neurodegenerative disease. The current review will discuss the different sources of stem cells in their preclinical and clinical application, as well as providing an overview as to the issues that need to be addressed to ensure a successful translation from bench to bedside.

Keywords: Neural Stem Cell, Embryonic Stem Cell, Mesenchymal Stem Cell, Transplantation, Brain, Neurological Disease.

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1. Introduction

A long-standing dogma in neurology has been that once brain cells are lost, they cannot be replaced. Notably, Ramon y Cajal [1] professed that: "Once development was ended, the fonts of growth and regeneration of the axons and dendrites dried up irrevocably. In the adult centers, the nerve paths are something fixed, and immutable: everything may die, nothing may be regenerated."

The dogma that emerged was that once development was complete and the brain reached maturity, the only option available to neurologists was to reduce the impact of damage. Therapeutics therefore only focused on limiting the progression of neurodegeneration. Despite some success at damage limitation, patients remain largely disabled with a poor quality of life and little hope for any reversal of symptoms. Slight improvements in deficits were ascribed to diaschisis, an undefined process in which existing neural networks take over new functions. Regeneration or transplantation of brain tissue that could reverse neurological damage was believed to be impossible.

2. Brain tissue transplantation – first steps

Up to the middle of the 20th century, only a very limited number of studies emerged in the literature that reported attempts to transplant various tissues into damaged brains (see Table 1 for a historical overview of neural transplantation). It was only in the 1970s that methods were refined to ensure a robust graft survival of transplanted tissues in the brain [2-4]. These early studies discovered that immature brain tissue shows better survival compared to adult brain tissue [5]. In vitro preparation and injection techniques were also refined to ensure that transplanted cells were still viable upon implantation [6]. It was also noted that the brain is an immunoprivileged site and that this actually results in a better survival of grafts compared to the same tissue being transplanted into peripheral sites [7]. The seminal study by Perlow et al [8] in an animal model of Parkinson's disease provided the basis for neural transplants to serve as potential therapy for neurological disease.

Motor symptoms in Parkinson's disease (PD) are mainly due to a loss of dopamine availability in the striatum. Grafted cells can therefore simply function as a pharmacological pump that restores dopamine levels. For this, cells are implanted ectopically into the striatum, rather than the substantia nigra where the disease kills off dopamine cells that project to the striatum. To this end, for instance, dopaminesecreting adrenal medulla tissue can be transplanted to restore dopamine levels in the striatum. Proximity to the choroids plexus is key to this approach to ensure that grafts get sufficiently vascularised to support its metabolism [4]. No synaptic integration of the graft with the brain tissue is necessary to exert beneficial effects. The advantages of this approach are that autologous tissue can be used to avoid the risk of graft rejection. Moreover, sufficient tissue is available to perform bilateral transplantation[9]. A series of clinical trials have been

Year	Researcher	Milestones
1890	W.G. Thomson [287]	Transplantation of adult brain tissue between two dogs
1898	J. Forssman [288]	Observation of trophic effect of grafted tissue
1907	G. Del Conte [5]	Grafting of embryonic tissue into the brain
1909	W. Ranson [289]	Grafting of spinal ganglia into the brain
1911	F. Tello [290]	Grafting of peripheral nerve into the brain
1917	E.H. Dunn [291]	Neonatal rat neocortex grafted into adult rat brain
1921	Y. Shirai [7]	Brain recognised as immunoprivileged
1924	G. Faldino [292]	Grafting of fetal brain tissue to anterior eye chamber
1940	W.E. LeGros Clark [293]	Embryos used a tissue source for neural grafting experiments
1944	D. Woolsey [294]	Unsuccessful transplantation of medullary tissue into humans
1945	H. Greene [295]	Transplantation of human cerebral tissue into an animal
1957	B. Flerko [296]	Intraventricular grafting of endocrine tissue
1962	B. Halasz [297]	Transplantation of endocrine tissue with improvement of function
1970	L. Olson [6]	Histological characterization of grafted fetal brain tissue
1974	B. Hoffer [3]	Electrophysiological evaluation of functional specificity of transplanted neurons
1976	U. Steveni [4] A. Björklund [2] R. Lund [298]	Establishment of methods to ensure robust graft survival
1979	H. Goldsmith [167]	Transplantation of oemental tissue in patients with stroke
1979	M. Perlow [8]	Fetal tissue transplants beneficial in rat model of PD
1985	E.O Blacklund [299]	Unsuccessful fetal tissue transplants in human patients with PD
1987	I. Madrazo [10]	Transplantation of adrenal medulla cells into patient with PD
1990	O. Lindvall [300]	Unequivocal benefit of tissue transplant demonstrated in PD patients
1992	E. Snyder [301]	Transplantation of neural stem cell line into mouse cerebellum
1997	T. Deacon [302]	Xenotransplant of porcine tissue into patients with PD Fetal tissue transplants into HD patients
1998	J. Thomson [303]	Generation of human embryonic stem cell line
1999	E. Gould [64]	Demonstration of in vivo neurogenesis in adult primate brain
2000	D. Kondziolka [130]	Transplantation of postmitotic neuroteratocarcinoma cells in patients with stroke damage
2001	C. Freed [35]	Double-blind trial of neural transplants in patients with PD
2002	L. Björklund [140]	Transplanted embryonic stem cells recover function in animal model of PD
2006	J. Zhu [304]	In vivo visualization of transplanted cells' migration in patient with brain trauma by cellular MRI
2007	K. Takahashi [59] M. Wernig [60]	Reprogramming of fibroblasts into an embryonic stem cell-like state

Table 1. Historical overview of milestones relevant to the development of neural transplantation for neurodegenerative disease.

conducted showing some benefit to patients with PD [10-14]. However, adrenal tissue only poorly survives in the brain [14,15] and recovery is thought to be more associated with a rejection or dying of the tissue than its survival [16]. In some cases, the procedure itself even resulted in post-operative mortality [17]. This approach has been mostly abandoned in favour of transplantation of cells derived from fetal brain tissue.

The introduction of fetal ventral mesencephalic tissue grafts in the mid 1980s was based on a few animal studies that demonstrated the efficacy of this tissue [18]. As tissue was derived from aborted fetuses, these initial clinical studies [19-21] were met with some controversy about having a clear separation between the decision to terminate a pregnancy and the use of fetal cadaver tissue [22,23]. Although great excitement surrounded these clinical trials, a lack of controls and standardization between trials made it difficult to interpret the reliability of these results. A common framework of assessment that was to be adopted by all clinical trials of neural transplants in PD, the Core Assessment Program for Intracerebral Transplantation (CAPIT), was developed to ensure that the efficacy between trials can be compared [24]. In general, clinical trials demonstrate positive clinical outcomes [25,26] including good graft survival and differentiation in post-mortem examination [27-29] and positron emission tomography (PET) [30-33]. However, in some cases dyskinesias developed after transplantation [34]. The first randomized double-blind clinical trial of fetal tissue transplants indicated that there was no benefit of the grafts over sham-surgery 12 months following implantation [35]. There was some benefit though observed in younger patients (<60) in the morning prior to medication. However, the reason why there is a difference between younger and older patients remains the subject of speculation as both groups showed a 40% increase in F-DOPA uptake on PET scans [36]. Still, there was only a significant correlation between F-DOPA uptake and clinical outcome in younger patients. This trial also shed some light on the development of post-transplant dyskinesias [37]. Although critiques were raised regarding the design and methods used in this trial [38,39], it raises important questions as to the reliability and efficacy of this treatment approach.

Despite the relative success of fetal tissue transplants to alleviate symptoms in Parkinson's disease, these initial fetus-derived grafts are associated with considerable limitations. Notably, the source of the tissue is highly unreliable, as it is dependent on the availability of aborted tissue that is of the right developmental time window [40]. About 6-8 donors are required for a unilateral transplant. As all of these might have different immunological profiles, it is not possible to match donor and host. Fetal tissue transplants are also highly heterogeneous in composition containing blood vessels and microglia, in addition to neural stem cells and partially differentiated cells. Although the inflammatory response associated with graft rejection due to recognition of MHC molecules on blood vessels and microglia can induce some recovery [41], it is generally assumed that the therapeutic entity in fetal tissue grafts consists of neural stem cells that can differentiate into site-appropriate phenotypes. Increasing efforts were therefore geared towards purifying the source of transplant material and to generate cell lines that would consist of a homogenous population of clonal cells that all have the same properties [42,43]. Preferably, these cells would be multipotent, i.e. able to differentiate into neurons, astrocytes and oligodendrocytes. These properties are ascribed to neural stem cells (NSCs) during development. NSCs might therefore provide an ideal source of transplant material.

3. Refining the sources for neural transplantation

The collective term "stem cell" is used to describe the type of immature cell that gives rises to mature specialised cells during development (see Table 2 for some useful definitions). These stem cells can be derived from the embryo, foetus and even adult. Tissue-specific stem cells, such as neural stem cells, typically have a more restricted developmental potential than embryonic cells. In normal development, these tissue/organ-specific stem cells will only give rise to cells forming one particular organ system, such as the CNS.

Concept	Definition
Stem Cell	A type of immature cell that is at least multipotent. Given the right circumstances, this cell can proliferate without differentiating, but can also differentiate into appropriate phenotypes.
Progenitor Cell	A type of cell with a more restricted potential than stem cells, typically giving rise to only 1 or 2 phenotypes.
Potency/Potential	The capacity of an immature cell to differentiate into different types of cells.
- Totipotent	The capacity of a cell to produce all cells necessary to generate a new organism (incl. placenta).
- Pluripotent	The capacity of a cell to produce all the cells necessary to produce multiple organ systems needed for a whole organism (excl. placenta).
- Multipotent	The capacity of a cell to produce multiple types of cells within the same organ.
- Bipotent	The capacity of a cell to produce 2 different types of cells.
Specification	The autonomous development of a cell in isolation to become a particular phenotype. This phenotype can be changed by environmental factors.
Determination	The autonomous development of a cell in isolation to become a particular phenotype irrespective of its environment.
Cellular plasticity	A cell's ability to adopt different phenotypes depending on environmental cues.
Transdifferentiation	A cell's ability to produce cell phenotypes that typically are not within the same lineage.
Fusion	Two cells integrating with each other to produce a new cell that contains elements from both parent cells.
Isolation	Removing cells from their natural environment
Purification	Ensuring that a particular cell type is enriched within a heterogenous mix of cells
Selection	Identifying a particular type of cell and removing it from a population of cells
Characterization	Defining the attributes/markers that define a specific cell type

Table 2. Useful definitions related to cell transplantation studies.

Neural stem cells

As with fetal tissue transplants, NSCs are initially derived from fetal brain tissue. Efficient in vitro protocols have been established to isolate NSCs from dissected fetuses. Typically, the brain tissue from an E14-E16 mouse/rat foetus is used for this. To derive human NSCs, aborted tissue from 8-10 week old fetuses are generally used. The neurogenic time window is an important aspect here. Use of fetal material that is earlier in development is unlikely to provide a high yield of neural cells, whereas tissue from a later developmental stage is more likely to produce glial cells[44]. Although it is possible to isolate neural stem cells and progenitors from the neonatal and adult brain, the yield is far lower and is often too low for transplantation studies. Self-renewal and multipotentiality to differentiate into neurons, astrocytes and oligodendrocytes are the key characteristics of NSCs (Figure 1).

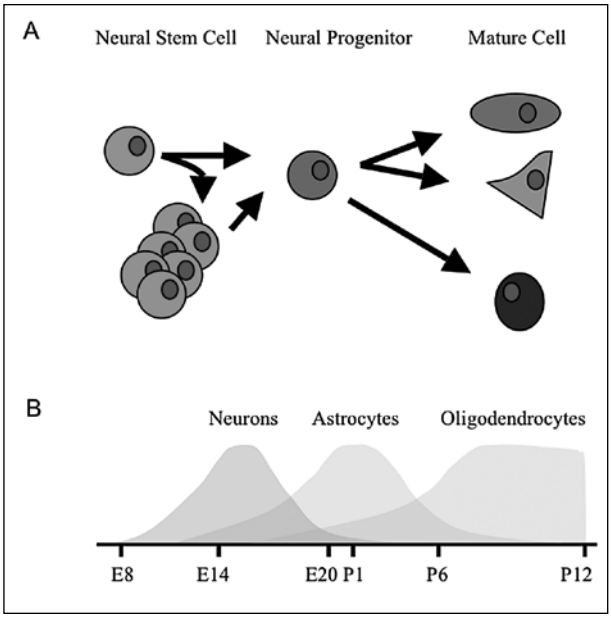

Figure 1. Neural Stem Cells. A. Neural stem cells (NSCs) are multipotent cells that can self-renew, but can also differentiate into neurons, astrocytes and oligodendrocytes (A). The neurogenic period in the brain starts around E8 and is significantly reduced by E20, whereas astrocyte differentiation is highest around E20 in rat/mouse (B). Oligodendrocytes are generated later in development and differentiation continues post-natally. The optimal time for derivation of NSCs therefore is during the peak neurogenic period.

At present, no specific NSC marker exists, but NSCs are defined by a combination of immunohistochemical markers (see Table 3 for markers that distinguish various types of stem cells relevant to brain repair) and functional properties. Factors that control the self-renewal of NSCs are, for instance, FGF, EGF, and TGFalpha[45]. Regional differences in isolation can lead to specification of cells[46], such as mesencephalic tissue giving preferentially rise to dopaminergic cells. Positional specification and cellular determination play a crucial role in this preferential differentiation. Most cells that are derived from primary tissue will eventually spontaneously differentiate or undergo differentiation. Increasing the number of passages also affects the cells'differentiation and survival characteristics[47,48]. One

Stage		Cell Type	Marker	
			+	-
Development		ESC	Oct-4 Nanog SEEA3 SEEA4 HLA class 1 Thy1 (CD90)	Nestin Sox2 Prox1
		NSC	Nestin Sox2 Prox1 CD133	Oct-4 Nanog NeuN/MAP2 GFAP* O4
Adult	**SEZ**	A – Neuroblast	Dlx PSA-NCAM	GFAP
		B – Astrocyte	GFAP S-100b	Dlx PSA-NCAM
		C – Transient amplifying	Dlx	GFAP PSA-NCAM
		E – Ependymal Cell	CD133	GFAP PSA-NCAM
	GZ	G – Granule Cell	PSA-NCAM	GFAP
		B – Astrocyte	GFAP S-100b	PSA-NCAM
		D – Precursor	PSA-NCAM	GFAP

Table 3. An overview of stem cell markers relevant to the brain.

approach to overcome these limitations is to genetically modify isolated NSCs to produce clonal cells that are conditionally immortalized. The advantage here is that the proliferation and differentiation of the NSCs can be regulated by changing the environment[42]. Despite a low immunogenicity[49,50], these NSCs still harbour a risk of immunological rejection when transplanted into patients[51]. Therefore, neural stem cells that are immunologically compatible with a patient would be preferable. However, autologous NSCs are difficult to obtain and therefore the derivation of embryonic stem cells by means of therapeutic cloning could provide a promising avenue to obtain cells that will not undergo a rejection upon transplantation.

Embryonic stem cells

As the prototypical stem cells, embryonic stem (ES) cells are totipotent and can produce any type of cell that is needed in the development of an entire organism (incl. placenta). These cells are only present in a blastocyst, where they can be derived from the inner cell mass (ICM) (Figure 2). Pluripotent ES cells are slightly more restricted in their potency and cannot give rise to the embryonic membrane,

but can give rise to all organ systems. The regulation of potency and 'stemness' has been the topic of intense investigations to find a common set of genes that would allow screening of cells for their potential therapeutic applications [52-54]. Commonly accepted markers for ES cells consist of POU5F1 (a.k.a. Oct-4) and Nanog (see Table 3), but a series of other markers has recently been identified by the International Stem Cell Initiative [52] that compared 57 ES cell lines. These markers can in the future potentially provide a fast and robust method to determine if a particular line is an ES cell line or not.

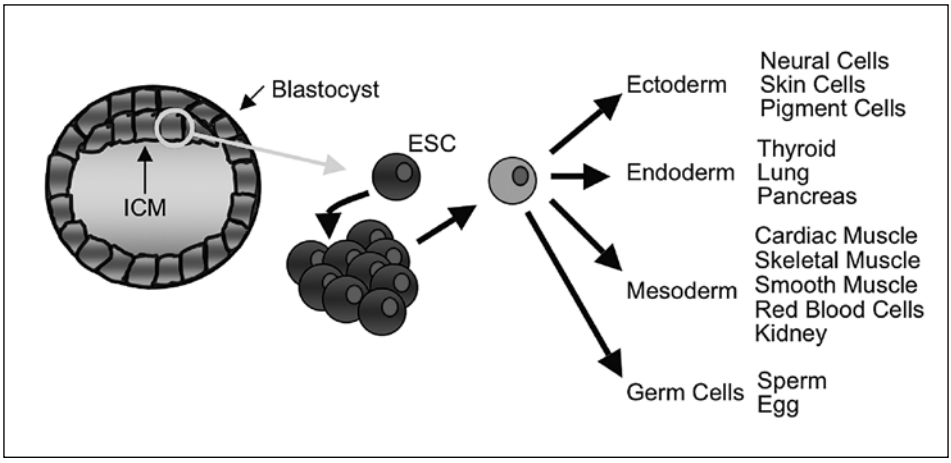

Figure 2. Embryonic Stem Cells. Embryonic stem (ES) cells are derived from the inner cell mass (ICM) of the blastocyst. These ES cells can be potentially be propagated indefinitely in vitro using the right mix of growth factors. However, given the appropriate conditions these cells can differentiate into any type of cell that can be found in a developing or adult body. These multipotent 'master' cells are therefore the most interesting in terms of cellular repair strategies.

Since their derivation from the mouse [55,56], the generation of ES cell lines is steadily progressing. Most of these lines are derived from supernumerous embryos derived through in vitro fertilization. These cell lines will not provide a source for autologous transplants, but by creating sufficient cell lines (150 cell lines would cover 20% of the population) it would be possible to immunomatch some individual patients to a cell line [57,58]. These cell lines could be banked for distribution similar to blood banks. Although these cell lines might not provide a perfect immunological match, it is thought that in many progressive disease states, it is unlikely that patients could derive benefit from their own cells, as these might also be susceptible to disease. Until recently, somatic nuclear transfer (i.e. therapeutic cloning) has been considered the main technique to generate autologous ES cells (Figure 3), but several groups have recently demonstrated that it is possible to reprogram somatic cells, such as skin fibroblast, to adopt an embryonic stem cell-like state [59,60]. This technique would provide a source of ES cells that is both

ethically acceptable to most people and provide autologous transplant material for those patients that would benefit from this (e.g. stroke patients). Nevertheless, transplantation of ES cells incurs a high incidence of tumours. Teretocarcinoma formation upon implantation of ES cells in a neonate is, for instance, a functional assay to verify that ES cells are indeed ES cells[55]. Hence to repair the brain, ES cells typically are progressed to the NSCs stage at which they can be transplanted without a major risk of tumor formation. Factors that regulate the progression from ES cells to NSCs either mimic the environment of the neuroectoderm or reduce cell density that induces a default progression to NSCs[61,62]. These cells typically require LIF as a survival factor to transform ES to NSCs, while BMP4 inhibits neural differentiation of the NSCs. In contrast, BMP antagonists, such as noggin, will enhance neural differentiation of NSCs[63]. Still, transplantation of neural stem cells could, become obsolete if the brain's endogenous neural stem cell pool could be mobilised and effectuate repair.

4. An endogenous neural stem cell niche – the fall of a dogma

Although by the 1990s, transplantation of cells into the brain was established as a potential clinical treatment, the concept that the brain would continuously produce new neurons was still very controversial. Ultimately, studies by Elizabeth Gould established that adult neurogenesis is not only relevant to the rodent, but also occurs in the primate brain[64,65]. The presence of neurogenic

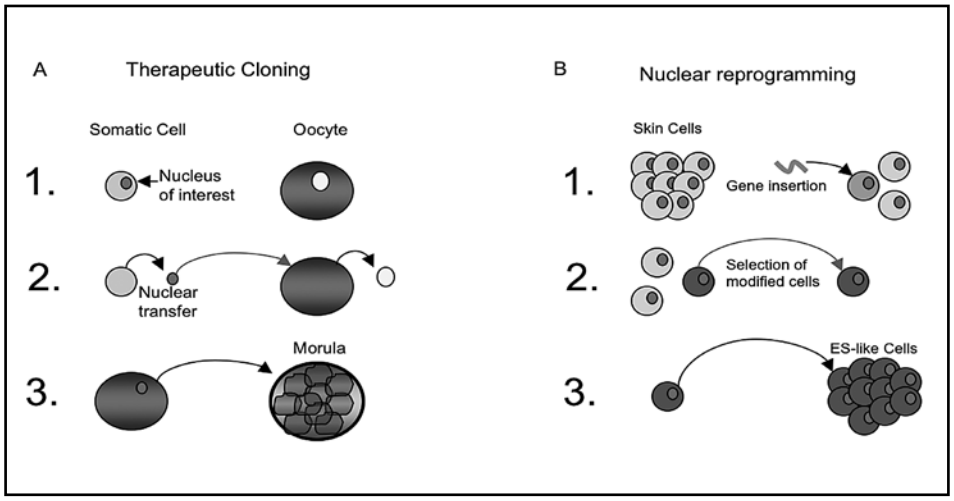

Figure 3. Therapeutic Cloning. To ensure that transplanted cells are not rejected, it is desirable to transplant autologous cells. To derive autologous embryonic stem cells it will be necessary to transfer the nucleus of a cells from the patient into an oocyte, so called therapeutic cloning (A). Once this has been achieved the embryo needs to develop to the stage of forming an inner cell mass from which ES can be derived. Alternatively, a gene can be inserted into somatic cells that effectually regresses the cell to the ES stage (B). This form of nuclear reprogramming then can select and expand the regressed ES cells to provide a sufficient source for transplantation.

regions in the adult brain therefore brought to fall Cajal's dogma that nothing can regenerate in the adult brain[66]. Administration of 5-bromo-3'-deoxyuridine (BrdU) labels all dividing cells, i.e. also self-renewing neural stem cells, during the S-phase of mitosis. A major advantage of this technique over other techniques, such as [^{3}H]-thymidine, is that it can be visualised using immunohistochemical techniques rather than autoradiography[67]. Two major regions of adult neurogenesis are distinguished today, notably the subependmal zone (SEZ) and the dentate gyrus (DG) in the hippocampus (more specifically the subgranular zone, SGZ).

The subventricular/subependymal zone

The mammalian CNS at the earliest stages (E11 in mouse) is initiating an asymmetric division progressing from a symmetrically dividing stem cell pool[68]. This asymmetric division is a crucial feature of neural stem cells during this stage as it allows the stem cell pool to be replenished, whilst at the same time providing progenitors that will give rise to the different brain structures (Figure 4). As the fetal development of the brain progresses, the neural stem cell niche is being confined to the subventricular zone (SVZ). During brain maturation, this region is undergoing some structural and functional changes. In adults, this region is known as the subependymal zone (SEZ) which lies adjacent to the ependymal cell layer that is lining the lateral ventricles. This 'neural stem cell niche' is a highly organised anatomical unit that contains different types of cells that govern adult neurogenesis (see Table 3). This process is highly conserved across species[69,70]. There is

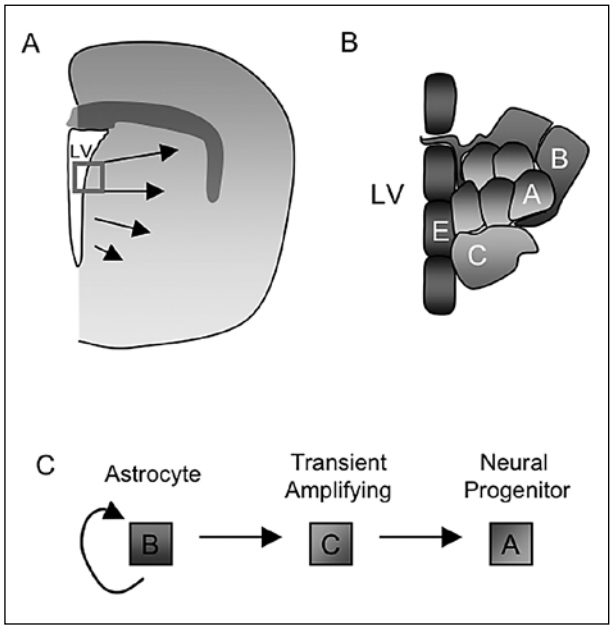

Figure 4. The endogenous neural stem cell niche. The subependymal zone (SEZ) is located adjacent to the ependymal zone that is lining the lateral ventricle (A). The SEZ is highly organised (B). The current thinking is that the SEZ-resident astrocyte transforms into a transient amplifying cell that proliferates before differentiating into a progenitor (C). It is then the progenitor cells that will leave the SEZ and colonize the brain to undergo terminal differentiation.

an ongoing debate as to the true identity of the NSCs residing in this area[71]. It remains unclear if the true SEZ neural stem cells are a subfraction of CD133+ ependymal cells[72] or GFAP+ astrocytes in the subependymal zone[73].

Neurogenic regions aplenty

Although initially only the SEZ and subgranular zone (SGZ) form the dentate gyrus in the hippocampus were identified as neurogenic regions in adults, a multitude of other regions have now been identified as producing some neurons throughout life[74]. There is a growing body of evidence that adult neurogenesis is involved in a variety of psychiatric[75,76] and neurological conditions[77,78]. In some neurodegenerative diseases, it is the poor response of endogenous neurogenesis which is exacerbating the disease condition[79]. A successful therapeutic intervention therefore is likely to involve some modification or mobilization of the endogenous neural stem cell pool. This mobilization of endogenous stem cells could be achieved using pharmaceutical approaches, such as anti-depressant[75] or anti-psychotics[76], but can also be achieved by growth factors that can be secreted by transplanted stem cells that are derived from peripheral tissues, such as the bone marrow.

5. Finding alternative sources to promote repair

Although replacement of lost neurons is considered to be the main therapeutic strategy to recover lost functions, other mechanisms, such as growth factor delivery or immunomodulation (see Table 4 for mechanisms of grafts), can also achieve effective functional improvements.

Bone marrow stem cells

In the adult bone marrow, there are typically three fractions of cells: endothelial, hematopoetic (HSC) and stromal (or mesenchymal) stem cells (MSCs). However, the focus of interest has mainly been on MSCs in terms of brain treatment. MSCs are fibroblast colony-forming cells that can generate bone (osteoblasts), cartilage (chondrocytes), myelosupportive stroma and adipocytes[80]. Only 0.001-0.01% of cells from the bone marrow are MSCs. Isolation and purification of cells derived from the bone marrow still need some refinement as presently a largely heterogeneous mixture of cells is derived in which about 10-20% show mulipotentiality and the remainder being of a committed phenotype[81]. Upon intravenous injection, some of these cells will enter the brain and differentiate into microglia and astrocytes[82]. In vitro, these cells can also be induced to express markers commonly associated with neurons[83], but it is unclear if these are functionally truly neurons[84]. It has also been reported that MSCs differentiate into neurons in vivo[85], despite less than 2% of cells entering the CNS[86]. Typically, only a small fraction of intravenously injected cells enter the brain with the large majority being retained in the lung and liver.

Mechanism	Description	Examples
Pharmacological	Grafts secrete deficient neurotransmitters or neurohormones	Dopamine secretion by striatal grafts in PD patients
Cell replacement	Grafts replace lost cells and restore	Grafted cells replace lost CA1 neurons in ischaemia-damaged hippocampus
Neurogenesis	Grafts stimulate endogenous neurogenesis	
Trophic factors		
- *Anti-apoptotic*	Grafts prevent further cell death	NSCs improve dopaminergic cell survival in Substantia Nigra
- *Plasticity*	Grafts support re-organisation of host networks	Adrenal grafts secrete factors that induce axonal sprouting
- *Differentiation*	Grafts support differentiation of endogenous stem cells	
Endogenous proteins	Upregulation of developmental proteins that aid reorganization of host tissue	Upregulation of ApoE after transplantation
Immune response	Immune response clears grafted cells and delivers inflammatory cytokines that enhance recovery	Rejection of medulla grafts associated with recovery
Immunomodulation	Grafted cells modulate the immune response either directly or indirectly to reduce damage	Atonement of immune response in model of EAE
Bridge	Grafts provide cellular substrate for regeneration of host axons	Peripheral nerve segments allow regrowth of CNS axons in optic or spinal cord pathways
Reinnervation	Grafts provide synaptic reinnervation and tonic reactivation of host brain	
Reconstruction	Grafts establish input and output connections with host brain that restores functional neural circuits	Striatal grafts reconstruct cortico-striato-pallidal circuits in HD
Non-specific		
- *Side-effect of surgery*	Surgery creates small damage that exerts a beneficial effect	Caudate lesions alleviate PD symptoms
- *Placebo effect*	Expectation of treatment effect produces an improvement in behaviour	Sham transplant improves function in PD patients

Table 4. A list of putative mechanisms of neural grafts.

Umbilical cord cells

Human umbilical cord cells (HUBC) are derived from the umbilical cord blood of newborn babies. It is very similar in composition than peripheral blood. The low immunogenicity of cord blood cells compared to peripheral blood or bone marrow cells is thought to be due to the abundance of immature progenitors that have longer telomeres and generally express fewer MHC antigens [87,88]. The main difference to bone marrow cells is that HUBC have a lower content of lymphocytes [89] and a higher proportion of CD34+CD38-hemtopoietic stem cells (HST) [90]. However, another significant difference to bone marrow is that insufficient cells can be gained from a single cord to transplant 1 patient, therefore a combination of different blood is needed. Considering that for bone marrow transplants only about

20-25% of people find immunocompatible cells, it will be necessary to develop expansion methods that will allow sufficient cells for transplantation. Expansion can be achieved using stem cell factor (SCF), FLT3L, thromboproietin, IL-8, VEGF and glycoaminglycan[91]. However, this expansion might change cellular properties and careful assays will need to be conducted at the end of the expansion to ensure phenotype consistency. In the presence of the appropriate factors (e.g. retinoic acid), these cells can also be induced to express brain-related proteins, such as Musashi-1, TUJ-1, GFAP[92,93]. Nevertheless, only very few transplanted cells will adopt a neuronal phenotype in vivo[94] and it is therefore thought that the main therapeutic benefit derived from HUBC transplantation will be due to growth factor secretion or immunomodulation.

Amnion-derived cells

The amniotic ectoderm is derived from the epiblast on the 8th day of fertilization. Amniotic epithelial cells might maintain their plasticity. The amnion is adjacent to the trophoplast cells and defines the amniotic cavity. It is composed of a single epithelial layer, a thick membrane, and an avascular mesenchymal layer[95]. The amion is supplied with nutrients and oxygen through the amniotic fluid, the chorionic fluid and vessels from the fetus. Typically, human amniotic epithelial (HAE) and human amniotic mesenchymal cells (HAM) are derived from the amnion as these cells represent pluripotent cells that can give rise to all 3 germ layers. Amniotic fluidderived cells have a similar pluripotent potential. The cells exhibit markers that can also be found in ES cells, such as Oct-4 and Nanog[96,97]. These cells therefore would represent an abundant source of cells as they can be derived upon parturition from the placenta that would not raise ethical issues. Cells derived from the amniotic-fluid have also been demonstrated to have the potential to differentiate into a variety of cell lineages[98]. Amnion-derived cells have been shown to have anti-inflammatory and anti-angiogenic properties[99]. HAM cells also express markers typically associated with neural stem cells, such as nestin and musashi-1[100], whereas HAE cells synthesise and release acetylcholine[101], dopamine[102] and neurotrophic factors[103]. Despite expression of these markers, it is unclear if these cells indeed could replace neurons in a functional circuitry, although they certainly could be used for neurotransmitter replacement or trophic factor support. Fetomaternal microchimerism in which fetal cells invade the brain of the mother and differentiate into appropriate phenotypes[104] could potentially be linked to amnion-derived cells as there is a steady increase in fetal cells that can be found in the mother's brain from the day of parturition to 4 weeks post-partum. If this would be the case, it would be important to establish how this fraction of cells could be captured and expanded to be used for therapeutic purposes.

Adipose-derived cells

A fraction of cells that are aspirated by liposuction from human adipose tissue have been reported to have the in vitro potential to differentiate into adipogenic,

osteogenic, chondrogenic and myogenic cells [105]. However, a small proportion of cells, known as multipotent adipose-derived stem (MADS) cells, can also be identified [106,107]. Expression of Oct-4 and more lineage-specific markers suggests that these cells might developmentally be placed somewhere between embryonic and 'adult' stem cells [98]. These cells therefore would provide an autologous source of cells for transplantation [108] that can differentiate into a variety of mesenchymal stem cells [109]. Although these cells show some potential to differentiate into cardiomyocyte-like [110] and endothelial-like cells [111], no indication of neuronal differentiation has been reported today. Based on these cells' properties, the only CNS application therefore could be to stimulate neovascularization [112].

Olfactory ensheating cells

In the basal layer of the olfactory epithelium, olfactory neurogenesis is an ongoing process [113,114]. In the case of damage, this process is enhanced and effectuating repair. The mammalian olfactory system is the only neural tissue where axons grow throughout adulthood [115], but this regeneration is needed as olfactory neurons only survive for about 1 month [116]. It is thought that olfactory ensheathing glia (OEG) are the main factor responsible for this remarkable adult regeneration. Even within the spinal cord, OEG cells can integrate into areas of damage, whereas, for instance, Schwann cells cannot penetrate scar tissue. OEG reside in the olfactory nerve layer (ONL) organised in different lamina [117]. However, at present there are no specific OEG markers. These express a variety of immunohistochemical markers (e.g. P75, NPY, S100, GFAP, galectin-1, ß2-laminin) depending on their laminar distribution within the ONL. Within the olfactory bulb, OEG stay within their channel and do not migrate over wide distances [118]. However, upon implantation their behaviour is quite different. It is thought that OEG provide a scaffold system along which axons can regrow. This notion has been supported by in vitro experiments demonstrating that OEG stimulate axon outgrowth [119]. Neurotrophic factors, such as BDNF, GDNF, and NGF [120,121], in addition to ECM molecules, such as laminin and fibronectin [122], are known to be secreted from OEG. These factors are similar to other cells, but these typically do not have the same regenerative potential. It is, however, possible that the combination of factors and their different levels of expression could provide a specific mix that is more supportive of axonal regeneration after OEG transplantation than for other cells. An increase in angiogenesis after OEG transplantation has also been reported [123,124] and could potentially provide another scaffold system that could support nerve regeneration. It has also been suggested that OEG can achieve remyelination [125], a process they do not exhibit in their natural environment in the olfactory bulb. However, there is conflicting evidence regarding this [126]. As OEG can easily be harvested from the olfactory cavity in patients, they provide a source of autologous regenerative cells that could find multiple applications [127]. However, the absence of good markers that allow a reliable identification and selection of OEG might hamper rapid progress and ensure that only regenerating cells are transplanted. Clinical

studies using OEG (see below) so far have met with equivocal results indicating that further refinements in methodology will be needed to make sure this approach can produce reliable results.

Cancer Cells

The continued division of immature cells is not only a feature of stem cells, but is also a cardinal property of cancer cells. Teratocarcinoma cells, for instance, have the potential to differentiate into all 3 germ layers and typically are not forming metastases. This is similar to the testing of embryonic stem cells upon implantation into a rodent, where they will form teratocarcinomas containing all 3 germ layers. It is noteworthy that in both types of cells differentiation will result in a loss of tumorformation. It has therefore been postulated that potentially cancers arise from endogenous stem cells that were lacking the right stimulatory environment to induce differentiation. Providing these so-called cancer stem cells with the appropriate chemical environment differentiates these mitotic cells into post-mitotic cells. One cancer cell line, the NTera2/D1 teratocarcinoma (NT2-N) cell line, possesses these features and was derived from a testis teratocarcinoma [128] from which subclones for the different purposes have been generated [129]. Upon transplantation, these cells will generate tumours in 100% of animals. In contrast, if they are rendered post-mitotic by pre-treatment with retinoic acid (RA), the cells do not generate tumours and have even been found to be safe after transplantation in humans [130]. Nevertheless, more than for any of the other cell sources, the cells' safety in terms of tumour formation are a great concern, although this is mainly due to the origin of the cells rather than their biological properties [131]. Similar to ES cells, undifferentiated NT2 cells express markers, such as SSEA-3 and SSEA-4, but there are no reports regarding Oct-4 or Nanog expression. Typically, the nucleus of the NT2 cells is irregularly shaped and allows their identification even in the transplanted human brain (115). However, marker expression of NSC (e.g. MAP, NCAM, NGF) can also be found in undifferentiated cells. It is possible that this extensive and varied marker expression is a testament to the variety of cells NT2s can differentiate into. To ensure that NT2 are post-mitotic (so called hNT cells), they are treated for at least 3 weeks with RA upon which they will also start to adopt a neuronal-like morphology (29, 33). These differentiated cells express a variety of neurotransmitter markers (e.g. choline, serotonin, GABA, catecholamines) (63-66), but do not express GFAP (29). Nevertheless, little is known if the cells integrate functionally into neuronal circuits. The NT2 cell line represents an ample supply of human cells that can be used for transplantation without destroying an embryo.

6. Probing clinical potential

Transplantation or infusion of stem cells is ultimately aimed at improving functional outcome in patients. To ensure the safety and efficacy of stem cell trans-

plants preclinical studies in animal models of disease are required to reduce the risks that patients are exposed to. To evaluate the significance of these preclinical studies, it has to be considered that animal experiments are only attempting to model human disease, they never completely replicate the human condition. Preclinical experiments are designed to provide a proof-of-principle that stem cells can affect functional outcomes caused by particular disorders, but upon clinical translation a risk remains that this therapy will not be efficient in humans. For instance, of 1026 compounds tested for stroke, none was found to be effective, despite most of them showing promising results in animals [132]. Guidelines, for stroke studies, have, for instance, been drawn up to improve the quality of preclinical studies and to ensure a better prediction of clinical success. Likewise, the CAPIT and CAPIT-HD guidelines for human transplantation studies have been developed to ensure a common basis that would allow comparisons [24, 133]. Pre-clinical studies will need to develop similar strategies to clinical trials that ensure blinded conditions, group allocation methods, as well as inclusion/exclusion criteria to ensure that findings will find clinical significance. A lack of or deleterious effects are often not published and contribute to an overly optimistic evaluation of stem cell therapy. A more systematic approach that encompasses testing of a dose-response relationship, the mechanism of action, and immunological aspects need to be instigated. To date, most of these studies are lacking, especially from the preclinical literature. Although in some cases it is suggested that almost every measurable parameter is changed by stem cells, none of these show a clear statistical correlation with behaviour. Currently, the most advances in both preclinical and clinical brain repair have been achieved for cell transplantation n Parkinson's disease.

Parkinson's disease

Preclinical studies are the fundament on which clinical trials are built in this area. The 6-OHDA model of Parkinson's disease has been instrumental in this process. Although it only induces an acute degeneration, the pathological effects, such as a destruction of 80% of dopaminergic cells in the substantia nigra and a consequent loss of dopaminergic innervation of the caudate putamen (striatum in rats), have provided the basis to investigate if restoration of dopamine-levels in the striatum are sufficient to reduce motor symptoms. Often only the rotational bias in this unilateral lesion model has been used to probe the functional significance, but it has proven to be predictive of the clinical significance of these interventions. More refined behavioural measures, such as the staircase test and operant conditioning, have also been used to probe the wider functional significance of dopaminergic transplants in the striatum [44]. There is a clear dose-dependent effect in that the number of surviving TH-positive cells strongly correlates with behavioural recovery [134]. However, in this case, it is not necessary to re-establish full levels of dopamine, but merely shift the dopamine levels from less than <20% to more than 20% to reduce behavioural impairments [135]. Similar observations have been confirmed in clinical studies, where PET has been used to assess overall activity

(by means of FDG-PET) or to specifically look at the dopaminergic cells that have been transplanted (using ^{11}C–raclopride PET) [32]. If cells are rejected or removed, the behavioural improvement will subside and impairments will re-emerge [136]. The ectopic placement of grafts has been of some concern as well, as the deficient circuit is actually not rebuild. Most efforts geared towards restoration f the SNc and the striatum have met with modest results, both in terms of anatomical and functional repair. Mostly these studies used bridge grafts aimed at guiding/attracting the fibres from the SNc [137]. Others have attempted to place grafts in both the striatum and SNc to restore dopamine levels in both of these sites [138]. Grafts in the SNc, however, could also aim to be neuroprotective and slow down the degenerative process [139]. However, ectopic transplantation in the striatum is currently the most commonly adopted procedure.

The placement of dopaminergic cells into the striatum requires that these cells are partially differentiated in vitro prior to transplantation. NSCs that are transplanted into the striatum will adopt a striatal phenotype that does not include dopaminergic cells. However, it has been demonstrated that, for instance, embryonic stem cells can differentiate into dopaminergic cells in vivo depending on their seeding density [140]. The tumour formation in 20% of animals is, nevertheless, too risky to adopt this approach. Predifferentiation is also a challenging undertaking as mostly only a small fraction of cells will adopt a dopaminergic phenotype. Various cocktails of growth factors, such as GDNF, as well as seeding density are essential to improve differentiation [141]. Additionally strategies, such as transfection with dopamine phenotype-inducing genes (e.g. Nurr1) and increasing neuronal yield through a neurosphere aggregation step, have also been adopted. Nevertheless, most of these approaches have met with moderate success. To gain a measure of success of these strategies, the dopaminergic phenotype needs to be contrasted to the total number of neurons and cells. Typically, about 4-10% of cells are dopaminergic (TH+) with about 30% of all cells exhibiting neuronal characteristics [142]. However, the markers being used to evaluate dopaminergic neurons are also noteworthy as many other types of cells express dopamine markers, such as tyrosine hydroxylase or the dopamine ransporter (DAT). Although some of the markers might only be transiently expressed, it is important to ascertain that this is indeed a dopaminergic neuron (i.e. electrophysiologically) or if these markers were only transiently induced by the differentiation procedure.

The continued survival is another aspect that needs to be assured for cell transplantation to be successful. Only a small fraction of cells survive upon implantation (<5-10% of grafted cells) [143]. Currently, a large number of cells is needed to achieve a sufficient survival to affect behavioural function. If cell survival could be raised to 10% this would dramatically lower the number of cells required for transplantation and provide a much more efficient procedure. Still, to date little progress has been achieved. The use of lazaroids, growth factors, blood and antiapoptotic agents have only minimally shifted the survival of cells [135]. It is important

here to note that this survival is not related to an immunological response, but is a process that is intrinsic to the grafted cells. Pre-differentiation of cells in vitro is a major aspect here. When cells attach and induce differentiation, they start to extend processes. Removal from the culture dish often disrupts these processes and cells will subsequently die. Transplantation of undifferentiated NSCs therefore in general achieves a better graft survival, but ectopic transplantation is unlikely to induce dopaminergic cells, unless cells were previously genetically engineered to this end. Overcoming the issue of dopamine differentiation and survival is currently probably the most challenging aspect to improve existing clinical approaches [135].

Nevertheless, there has also been hope regarding the potential of pharmacological agents that could upregulate endogenous neurogenesis to effectuate repair. Van Kampen et al [78, 144], for instance, recently suggested that compounds that act on the D3 receptor system, such as 7-OH-DPAT, will induce neurogenesis in the substantia nigra with dopaminergic differentiation. It was further suggested that this local repair was underpinning behavioural improvements, such as amphetamine-induced rotation. Nevertheless, an in vitro study by Milosevic et al.[145] indicated that D3 is unlikely the direct mechanism by which this local dopaminergic neurogenesis is regulated. It is, however, possible that an indirect mechanism is at play that either indirectly upregulates neurogenesis or dopaminergic differentiation.

Huntington's disease

The surgical procedure for transplanting cells into the caudate putamen is virtually identical to that for Parkinson's disease. The aim of the transplantation and the type of cells are quite different. For Huntington's disease (HD), a replacement of neurotransmitters is unlikely to be sufficient, but either a circuit integration of transplanted cells or a slowing down of the disease process is needed. Early preclinical experiments used feline fetal tissue into the kainic acid (KA)-lesioned striatum [146]. Until recently, the administration of toxins, such as KA, quinolinic acid (QA) and 3-nitroproprionic acid (3-NPA) have been the main tools to model the neuropathology and neurochemical imbalance that is the key feature of HD. Experimental evidence suggests that there is a differentiation of fetal tissue into appropriate phenotypes and some degree of integration and reconstruction of circuitry can be found. This evidence is further supported by studies that indicate electrophysiological integration of transplanted cells in striatal circuitry, restoration of cortical metabolism and responsiveness to dopamine agonists [147, 148]. These anatomical and functional improvements were also evidenced in motor and cognitive improvements. It is, however, unclear to what degree functional recovery is the product of cell replacement rather than stagnation of neurodegeneration. Roberts et al, for instance, demonstrated that there was a strong correlation between the progression of striatal atrophy and behavioural recovery, whereas there was no link to degree of damage [149]. This benefit was also evident on pharmacological

MRI scans where transplanted animals exhibited an intact signal transmission in response to a D2 agonist and untreated animals showed a loss of cortical inhibition [150]. There is further evidence of a neuroprotective effect in that proactive transplantation of NSCs can reduce the degree of damage caused by the toxins used to model HD [151]. So far, little evidence has emerged from transgenic models in this area [152].

It is noteworthy that autologous cells in HD are not likely to be a desirable source for transplantation as these cells will carry the gene mutation that causes HD. Therefore little experimentation has so far been done regarding autologous MSC transplantation. However, MSCs from different donors might provide some functional improvement, although only a very small fraction of cells enters the brain after i.v. administration. More extensive studies are required to assess what the therapeutic opportunities using MSC could be in HD, i.e. when will they need to be administered to be most effective and how often will they need to be administered to provide a long-term benefit.

Clinical trials using neural tissue, however, have already developed a solid basis on which future studies can build on [153]. The first clinical implementation of fetal tissue transplants in HD patients was reported 1995 in Mexico [154], but was swiftly followed by reports from the USA [27, 155, 156], France [157-159], and more recently the UK [160]. Fetal grafts participate in motor movement and their functional integration into the host circuitry has been demonstrated using functional MRI (fMRI) [161], magnetic resonance spectroscopy [162] and PET [27, 156, 159, 163]. Graft survival has been demonstrated in patients for at least 6 years with most neurons adopting a GABAergic interneuron phenotype (calretinin+, calbindin+), rather than GABAergic output neurons (DARPP32+) that are typically lost in HD [164]. To date, no double-blind trial has been conducted and most studies are designed to address procedural safety, rather than efficacy. It is hence not possibly to provide a clear assessment of the effectiveness of this approach for HD, although preliminary data is very optimistic [159].

As the striatal pathology in HD is in proximity to the SEZ, it is reasonable to assume that there will be an effect on neurogenesis. In patients with HD, there is evidence that there is a decrease in neurogenesis [165], although the DG mice exhibit an increase in transgenic HD [166]. Further studies need to more specifically address how the huntingtin protein influences neurogenesis. As it has been suggested that neurodegeneration is aggravated by a failure of neurogenesis [79], the use of pharmacological agents could regulate neurogenesis in the SEZ and provide some improvement. However, at present there is no experimental evidence to support this option.

Stroke

Stroke is a major societal burden as it is the most common cause of adult disability in the industrialized world. The main aim after a stroke is to restore blood flow

to the ischaemic area and to protect dying cells. In the 1970s, Goldsmith et al.[167] pioneered the transposition of omental tissue to improve blood flow and oxygen supply in patients with stroke. It is suggested that blood vessels from the omental transposition grow into the patient's brain to restore blood supply to the ischaemic area. This therapeutic strategy remains under investigation, but to date has failed to gain a widespread implementation. It is questionable as to how quickly this transposition can resupply the infracted area with blood supply as most cells undergoing ischaemia will be irreversibly damaged within minutes to hours after stroke onset. However, it is possible that the omental tissue also secretes growth factors or allows blood-borne macrophages/microglia to penetrate the brain to induce diaschisis. Clinically, the most likely benefit is that the transposition will provide an alternative blood supply to the brain that will avert recurring transient ischaemic attacks (TIAs). The crucial experiments that would address these issues are currently not available in the literature. As with PD and HD, early cell transplantation experiments used fetal tissue that was grafted inside the lesion cavity. In general tissue integration was poor, although functional benefits were observed. These could be further enhanced by environmental enrichment suggesting that integration of grafted cells possibly can be achieved using training or rehabilitation [168, 169]. Neuroteratocarcinoma (NT2) cells provided an alternative source of human origin for grafting that was readily available [170]. Behavioural improvements appear to be dose-dependent, but survival of only 124 cells can be sufficient to support behavioural recovery [171]. Some of these cells exhibited a cholinergic phenotype, but it is unclear to what degree cells integrated into the host parenchyma. This poor survival questions the assumption that the prolonged survival of cells is required to improve behavioural outcome. Poor survival of NT2 could be explained by the need to partially differentiate these cells prior to transplantation. Layton Bioscience took these cells forward in clinical trials attesting the safety of the procedure. Little evidence of a functional benefit was apparent even after transplantation of 6000000 cells [130, 172]. Only patients with a right basal ganglia stroke improved neuropsychological measures, such as the Rey complex figure test, but other patients performed comparable to stroke patients that did not receive cellular grafts [173]. No further trials using these cells in stroke patients have been announced due to a lack of efficacy [174].

Neural stem cells have also been shown to be effective after transplantation in animals with stroke damage. NSCs have been shown to even migrate from the contralateral hemisphere to the site of damage [175, 176]. Although several putative chemokines and their receptors have been identified to be involved in migration, it is difficult to demonstrate in vivo if the cells indeed use these substrates to migrate. It is further unclear if migration is relevant to recovery. Although migrating cells have the advantage of seeking out areas of damage, cells that migrate widely could also potentially be a problem if cells transform into tumours. However, to date there has been no report of tumour formation after NSC transplantation. Placement of cells can, nevertheless, influence what behaviours

are recovered. Intraparenchymal grafts have been reported to recover a different set of impairments compared to intraventricular grafts [175]. The underlying basis of this difference remains poorly understood, although the upregulation of ApoE has been implicated in this difference [177]. Transplantation of dead cells results in an enlargement of the lesion proving that the behavioural recovery is not merely due to the transplantation procedure or an inflammatory response [178]. To date, the only clinical trial using fetal tissue has been conducted using pig-derived cells. This trial was stopped after 3 patients due to complications, such as epileptic fits. Still there was no report of a zoonosis in these patients, but the problems were purely of a neurological/surgical nature [179].

There is a growing body of evidence suggesting that MSCs from the bone marrow can improve stroke-outcome [180]. MSCs have been demonstrated to reduce lesion volume, to preserve white matter and to induce peri-infarct angiogenesis [181]. MSCs also show extensive migration in the stroke brain after intrathecal or intravenous administration [182,183]. The mechanism by which these cells exert beneficial effects, however, remains poorly understood, although it is mostly believed to be a trophic effect rather than cell replacement. Recently, a clinical trial using bone marrow cells has been reported demonstrating the clinical potential of these cells in treating stroke [184].

Alzheimer's disease

The growing impact of an ageing population dramatically increases the number of people with mild cognitive impairment (MCI) and Alzheimer's disease. Although achectylcholine esterase (AchE) inhibitors provide some improvement in the early stages of the disease, there currently is no effective therapy to avert the neurodegeneration. Transplantation of cells to replace lost neurons is a viable option. Early studies using cholinergic fetal grafts in animals with toxin-lesions to the nucleus basalis of Meynert (NBM) provided some benefit [185-188]. These models, however, are poor representations of the ongoing degeneration that is occurring in Alzheimer's disease. The advent of transgenic models that would express both persenilin-1 (PS-1) and a variant of the human amyloid precursor protein (APP) are more akin to the molecular deficits that are observed in human patients. For instance, APP is known to induce gliogenesis in transplanted and newly born cells [189]. This leads to an increase in reactive astrocytes and scarring in the brain that further inhibits repair. This is further evidenced by a long-term decrease in neurogenesis [190,191]. However, the gliogenic effect of APP can be averted by administering phenserine (a cholinesterase inhibitor) as it reduces the level of APP [192]. Developing small molecules that can exert a neurogenic effect and increase neurogenesis in AD patients would therefore be a potential additional route that could enhance memory performance [193,194]. Just the ageing brain itself reduces neurogenesis as growth factors, such as FGF, are reduced. NSCs have also been found to improve memory performance in aged animals [195]. Their migratory

ability is an added advantage to ensure that widespread areas of cell loss will get re-seeded [196].

Alternatively, the levels of growth factors can be raised in aged brains by i.v. infusion of MSCs or other peripheral cells, but bone marrow-derived cells can also influence the progression of the pathology per se. Bone-marrow-derived microglia, for instance, have been shown to have an essential role in limiting the formation of plaque [197]. Additionally, strengthening blood vessels through endothelial progenitors can also improve functional outcomes. Peripheral endothelial progenitors have also been associated with an indication as to the disease progression [198]. Omental transposition has also been suggested to increase blood flow, and reduce plaque burden, although no effect on neurofibrillary tangles was observed [199]. Nevertheless, most research efforts are geared towards the transplantation of progenitor cells in transgenic mouse models.

Spinal cord injury

Spinal cord injury is a devastating traumatic event, mostly condemning survivors to a lifelong paralysis. Cell therapy can either be aimed at providing a bridge for axons to regenerate, to provide trophic support for this regeneration, or replace cells that have been damaged or lost due to the injury [200]. Peripheral nerve transplants support growth of axons [201], but it is unclear if this approach is truly effective in terms of functional repair. A clinical case study suggests a measured functional improvement in a patient with incomplete transection [202], but in patients with a complete spinal cord transection this approach has not been effective [203]. Olfactory ensheating cells (OECs) have proven to be more useful in rodent models and improved functions, such as hindlimb paralysis and respiration [204, 205]. In China, Portugal and Columbia, several hundred people have already received these transplants [203, 206]. The effectiveness of this is very questionable though, as these surgeries are generally not following the design of a clinical trial. At best, minor improvements are reported. Although the procedure for transplanting cells has been established to be safe[207], currently there is no evidence that transplantation of cells is effective and patients therefore should not be exposed to the risk of an operation.

Although OECs represent the most promising therapy for spinal cord injury, there is also the possibility to use NSCs to recover some lost functions. The aim here is to have NSCs in the lesioned spine to relay signals from the muscle to the motor neurons from the brain. Some improvement has been observed in rats [208, 209], but it is questionable if these changes would be clinically significant. The grafted cells might also stimulate the microenvironment with growth factors that reduce the glial scaring and improve nerve conductance in spared axons [210]. Support for this notion is gained from hematopoietic and mesenchymal stem cells that have reduced some of the impairments [211, 212]. In a small clinical trial with MSCs, the improvements were akin to spontaneous recovery [213]. However, if transplanted

cells could accelerate or improve this spontaneous recovery, it could provide some clinical benefit. Transplantation of activated macrophages into the lesion can actually also decrease lesion volume and provide growth factors that stimulate recovery in rats [214,215]. Transplantation of activated macrophages in Israel and Belgium in patients has also been shown to provide a minor improvement [216]. Still, a controlled phase II trial is needed to establish the reliability of these results. Cell selection might be an issue as in rats only a subgroup of animals improved and this recovery was similar to that seen with other cell types. The specificity of activated macrophages as a therapeutic agent therefore remains uncertain [217].

Multiple sclerosis

Demyelination of the central nervous system is an important component of multiple sclerosis (MS). Remyelination of axons is thought to potentially reduce symptoms and avert further degeneration. Early transplantation studies by Blakemore[218] suggested that remyelinatation of axons is possible. These studies provided the basis to identify different sources of cells that could re-myelinate, such as oligodendrocyte progenitor cells (OPCs), Schwann cells, neural stem cells, but also olfactory ensheating cells (OECs). Widespread re-myelination of diffuse lesions in the brain [219], but also focal lesions in the spine exhibit a degree of re-myelination that might be of clinical relevance [220]. Predominantly Schwann cells and OECs have been used for spinal cord lesion, whereas OPCs are mainly used for brain lesions. OPCs can be isolated during neurosurgical procedures, expanded and re-implanted [221]. Schwann cell progenitors are also increasingly becoming of interest as they demonstrate a better survival, migration and integration compared to Schwann cells [222]. The diffuse lesions in the brain pose a challenge in terms of administration. Despite the ability of progenitor cells to migrate wide distances, this might not be in sufficient numbers to achieve a sufficient level of remyelination in the lesions. Although, in principle intraventricular injection would allow a widespread distribution of cells, it does not appear to improve outcome [223]. Intravenous or intra-arterial injection is a less invasive alternative that ensures an extensive distribution of cells in selective areas of damage with concomitant functional benefits [224]. However, expansion of OPCs in situ and in vitro is challenging as they typically have a slower cell cycles as other progenitors [225]. To get sufficient cells for i.v. administration will depend on refining these procedures. Mesenchymal stem cells (MSCs) can exert an immunomodulatory role and deliver growth factors to the lesion and therefore are also of interest to MS. MSCs enter sites of MS plaques and integrate into the tissue in these sites reducing the impact of the disease [226]. It remains, however, doubtful that a functional integration is achieved. Effects are likely to be mainly mediated through secretion of particular factors. There is a growing body of clinical trials that either use MSCs or hematopoietic stem cells [227], but these studies mainly provide a proof of principle [228]. Although some studies indicate a long lasting suppression of inflammation and a consequent stagnation in brain atrophy [229,230], most trials lack the power to draw definite conclusions on efficacy [231-233]. Typically, MRI serves as

the primary outcome and hence provides a reliable and non-subjective measure of comparison [234]. A clinical phase III trial is currently underway that will indicate if autologous hemopoietc stem cell transplantation is an effective treatment in comparison to the best currently available pharmacological agent, mitoxantrone [235]. MSCs and hemopoietic stem cells, however, are unlikely to revert the damage, but only limit its progression. Remyelinating cells will need to reach a similar level of clinical development to ensure that damage can be reversed [236].

Motor neuron disease (MND)

The degeneration of motor neurons is the hallmark of both amyotrophic lateral sclerosis (ALS, aka Lou Gehrig's disease) and spinal muscular atrophy (SMA). These conditions can either benefit from cell replacement of the lost motor neurons or from trophic factor support that slows down neurodenegeration. Replacement of motor neurons is a daunting task as it necessitates a complete re-innervation of the corticospinal tract in ALS, for instance. Although ES cells can be induced to differentiate into functional motor neurons by retinoic acid (to neuralise cells) and sonic hedgehog (Shh, to ventralize cells) [237], it is unlikely that these cells would reconstruct the corticospinal tract. Nevertheless, a more modest aim, such as restoring some connections between the spinal tract and the muscle has been demonstrated [237,238]. Occasionally, these axonal extensions form neuromuscular junctions provide a partial recovery [239,240]. Transplantation of astrocytes can also reduce neuronal atrophy through scavenging of excitotoxic glutamate [241]. Trophic support (e.g. BDNF, CNTF, NGF, etc) supports survival of damaged neurons [242] and possibly can limit the progression of the disease, although its potential to reverse damage through enhancing endogenous repair processes (e.g. neurogenesis) are currently doubtful for MND [243]. Encapsulated cells overexpressing CNTF to prevent a rejection response significantly improved survival and motor function in the progressive motoneuronopathy (pmn) mouse providing hope for clinical applications [244]. In a small clinical trial this approach elevated CNTF levels in the CSF, but unfortunately did not result in a significant clinical improvement [245]. Trophic effects are also most likely the mechanism of action of bone marrow-derived cells that slow down disease progression in transgenic mouse models [246,247]. Transdifferentiation of bone marrow cells has here been shown to be an artefact of cell fusion with many cells having differentiated into microglia [248]. Transplantation of mononuclear cells from umbilical cord also slows down disease progression in SOD1 transgenic mice demonstrating that increasing microglia might be beneficial[249]. Periphery-derived cells have also found their way into early clinical trials which are mainly of a pilot nature assessing feasibility rather than efficacy [250-252].

Neuronal ceroid lipofuscinoses (NCL)

Pediatric metabolic storage diseases are characterised by a lysosomal accumulation of autofluorescent lipopigment, neurodegeneration and death. These neuronal ceroid lipofuscinoses (NCLs) are all, but one, caused by mutations in at least 7

genes that are inherited in an autosomal recessive manner. Enzyme replacement therapy (ERT) aimed at replacing the deficient enzyme has met with modest success due to difficulties with blood-brain barrier penetration [253]. Delivering cells into the brain to secrete a steady supply of the right enzyme and growth factors could therefore constitute an attractive alternative strategy. In this case, it is important that the cells are not autologous as otherwise they would carry the harmful mutation as well. Bone marrow-derived hemopoietic stem cells have survived in a canine [254] and lamb model of ceroid-lipofuscinosis [255], but did not improve functions or survival. The stage of pathology, however, might be a crucial factor that determines if improvements are observed or not. For instance, only pre-symptomatic infusion of umbilical cord blood cells improved outcome in patients with Krabbe disease (aka globoid cell leukodystrophy) [256]. Quite a few small patient studies have been conducted [257,258], but have not resulted in a significant advance in treatment. Neural stem cells are currently under investigation in Batten's disease [259], but there is a scarcity of preclinical studies that indicate that this approach can be efficacious [260]. Although at present no effective treatment exists for these infant patients, the rapid progression to clinical trials without supportive preclinical experiments has led some to question the ethics of this approach [261].

Brain tumors

Cancer cells share many features (e.g. self-renewal, multipotentiality) that are cardinal to ES cells. Many have whence speculated that potential cancer cells are stem cells that have lost their ability to differentiate [262,263]. Understanding the fundamental difference between these two types of cells can therefore provide useful insights into both tumour development and repair [264,265]. As brain tumours constitute a pathology of the CNS that is characterised by undifferentiated cells, it is possible that providing the appropriate chemical factors will differentiate these cells into post-mitotic cells. Transplantation of neural stem cells have demonstrated conclusively that NSCs migrate to tumour cells and that they offer some benefits [266-268], although it is unclear if NSCs induced differentiation. Engineered cells that will deliver toxic factors to tumour cells have also been used to track down invading cells [269]. NSCs can reduce edema and proliferation rate [266], but large tumours remain. It is conceivable that this therapy might be useful in conjuction with other therapies, such as gene, chemo-or radiotherapy. Engineered cells might offer new hope to a more targeted gene therapy in which either NSC or MSC can be modified to secrete cytotoxic agents that kill tumour cells [270,271]. CNS gliomas secrete strong angiogenic factors that recruit MSCs from the blood stream [272] indicating that i.v. administration of cells could allow a non-invasive, but biologically-targeted delivery [273]. Clinical studies using autologous hemopoietic stem cells have already been implemented and suggest that there is some benefit in children with recurring tumours, but patients with a macroscopic residual tumour do not survive [274]. Large appropriately designed trials will need to be conducted to adequately assess the potential of cell therapy for brain tumours.

7. Ethical considerations

Cell transplantation is associated with various ethical issues[275,276]. The most widely debated issue relates to the derivation of embryonic stem cells from embryos. Embryos that are generated using in vitro fertilization are produced to provide an assisted conception. The purpose of the creation of these embryos is therefore quite different from its use to generate embryonic stem cells. The concern of some people is that embryos should be considered as human beings and as such not be destroyed to develop a cell line. Of course, the same cells could be derived from early abortions, but technically this source of material is far less controllable in terms of material quality and developmental stage. Many would argue that early stage embryos do not have a sentient central nervous system and hence the embryo at this stage merely represents a collection of primitive tissues that should not receive the same protection than, for instance, fetuses that have developed a brain and sensory perception. The public's views on these issues vary widely across and within societies. These disparate views have led to various countries either adopting a liberal, but regulated approach, whereas others have imposed clear limits as to what is acceptable for research. Only a handful of industrialised countries, including Luxembourg, so far have not provided a legal framework for this research[277]. Although the generation of ES cells from skin or parenthogenesis might overcome the issue of embryo protection[278], it does not deal with the issue that each ES cells potentially could generate a new human. Differentiating between reproductive and therapeutic cloning is therefore important[279]. Although some people would take a strong stance against reproductive cloning, there is a growing consensus in most industrialized countries that derivation of ES cells through therapeutic cloning is necessary to develop effective cell therapies that will aid millions of patients. Of course, ethical consideration also needs to be given to patients that currently might not get the best possible treatment due to a lack of research on ES cells.

There are also some specific concerns related to the transplantation of cells. It has, for instance, been suggested that grafting cells from one person to another person's brain could transfer some of their identity and hence neural grafting would impinge on the patient's sense of who they are[280]. These speculations were further fuelled by an experiment in birds that demonstrated that if neurons from one species to another were grafted in the region responsible for birdsong, the animal would actually learn the singing from the cell's source rather than from the host[281]. This issue as well as xenozoonosis were specifically discussed in relation to xenotransplants for patients with stroke or Parkinson's disease[282]. However, to date apart of the birdsong experiment, there is no evidence that this indeed has any impact on the host's behaviour. Chimeric animals in which human cells are transplanted into the nervous system at the embryonic stage develop normally. The question, however, has been raised as to how much of an animal nervous system needs to be replaced by human cells before this brain would no longer develop

like its host, but rather than hat of the donor [283, 284]. So far there is no indication that this indeed would happen, rather the contrary. Human cells survive well in animal brain and adopt to the general architecture. There is some evidence that suggests though that human cells might not integrate as seamlessly into animal hosts than syngenic cells.

From a medical and scientific standpoint, the most acute ethical question is the conduction of early clinical trials [206]. Although there is a strong sense that stem cells revolutionise modern medicine, it is unlikely to be a panacea. Early examples of poor tissue selection, for instance, have clearly indicated the risk of tumorigenesis in patients. A too eager clinical implementation risks deleterious and possibly deadly effects of this treatment. It is therefore important that clinical trials are based on the best possible scientific evidence and not only on the available evidence [285]. Moreover, clinical trials need to be conducted to the highest standards. As transplantation of cells is a novel approach many of the caveats of this approach are not necessarily apparent [286]. It is the responsibility of the regulators and ethical committees to minimize the likelihood of iatrogenic complications.

8. Conclusion

Over the past 30 years, transplantation of cells into the brain has emerged as viable new treatment option for neurological disease. The discovery that immature cells in the brain can restore functional deficits has lead to the discovery of endogenous niches of neural stem cells that replenish the normal brain with neurons. This has

Preclinical	Clinical
Preclinical animal studies need to improve in design to provide a reliable measure of efficacy (e.g. blinded assessment, group assignment, power analyses)	Proof-of-principle in patients needs to be brought that cultured stem cells can effectuate a robust improvement in patients
Factors that affect graft efficacy need to be identified and controlled (placement, number of cells)	Refine clinical protocols to ensure cell quality and purity
Mechanisms by which stem cell exert beneficial effects need to be addressed	Establish a dose-response relationship
Immunological studies regarding the need of immunosuppression need to be conducted	Determine if immunosuppression will be required
A common basis of assessment needs to be established to allow comparison between studies	Robust serial neuropsychological and motor tasks need to be developed to allow long-term monitoring of graft effects (i.e. refinement of CAPIT)
Imaging markers of graft survival and efficacy need to be developed to allow a rapid clinical translation	Neuroimaging techniques need to be refined to allow a more detailed anatomical and functional assessment
Limits of therapy need to be established	Improve patient selection and clinical trial design (placebo vs no placebo)
Interaction with endogenous stem cell pool needs to be assessed	Establish techniques that will allow in vivo monitoring of transplanted and endogenous cells

Figure 5. Aspects that require progress in the next few years to ensure that cell transplantation is successfully implemented in clinical settings.

led to a reversal of the Cajal dogma that "everything may die, but nothing may regenerate" in the brain. Some of the psychiatric drugs might even influence this endogenous neurogenesis and be a pivotal part in the recovery from depression or psychosis. Increasing this neurogenesis might also harbour promising new avenues in neurological disorders. However, it is likely that insufficient cells will be mobilised from these niches to truly induce a significant recovery. Supplementation with transplanted cells might therefore still be required. Stem cells have hence truly revolutionised treatment options and the concept of pathology in neurology. Still, considerable experimental progress needs to be achieved over the next few years to allow a robust clinical translation (see Table 5). The next decade will prove if we can use these newly gained insights to improve patients' quality of life.

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Registre National de l'Infarctus LUCKY

(Luxembourg Acute Myocardial Infarction Registry): Les femmes moins bien soignées que les hommes?

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Abstract:

The national LUCKY registry (Luxembourg Acute Myocardial Infarction Registry) confirms for Luxembourg that transfer of patients with acute myocardial infarction for primary percutaneous coronary intervention (PCI) is very effective. However, while mortality is low after PCI, a third of the patients with acute myocardial infarction develop severe left ventricular dysfunction. This may in part be explained by relatively long time delays between onset of symptoms and opening of the infarct-related artery, despite short distances between hospitals (time is myocardium). Surprisingly, in comparison with men, women are younger, have a higher body mass index and receive less evidence-based therapies such as statins before and after myocardial infarction. In conclusion, PCI has substantially improved the treatment of acute myocardial infarction in Luxembourg, but all actors including the patient have to keep efforts high to minimize time delays.

Key words: acute myocardial infarction – primary percutaneous coronary intervention – national registry – time delays – gender specific differences.

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Résumé:

Objectif: Analyser les différences potentielles concernant la qualité des soins et les résultats obtenus avec les traitements mis en place pour les femmes et les hommes qui présentent un infarctus du myocarde.

Méthode: Les patients traités à l'Institut National de Chirurgie Cardiaque et de Cardiologie Interventionnelle (INCCI) par angioplastie primaire pour infarctus aigu sont inclus dans le registre Luxembourg Acute Myocardial Infarction Registry (Lucky) depuis février 2006.

Résultats: Les femmes sont plus jeunes par rapport aux hommes quand elles font un infarctus aigu du myocarde. Cela peut s'expliquer par le fait qu'elles reçoivent moins de statines malgré un BMI plus important et un taux de cholestérol élevé. Les délais de traitement sont identiques pour les hommes et les femmes. Ils sont en moyenne de 4 heures entre le début des douleurs et l'arrivée à l'INCCI. Les hommes reçoivent presque 2 fois plus souvent de Reopro que les femmes. Les résultats cliniques, les complications et les résultats échographiques sont comparables entre hommes et femmes.

Conclusions: Le registre national Lucky confirme pour le Luxembourg que l'angioplastie primaire a pu réduire de manière spectaculaire la morbidité et mortalité de l'infarctus aigu. Cependant, un tiers des patients garde une dysfonction sévère après infarctus. Il est possible que ce pourcentage puisse être diminué par une prise en charge plus rapide du patient. En ce qui concerne les femmes, il faut insister sur le fait qu'elles ne sont pas épargnées par l'infarctus et qu'il faut les traiter de manière aussi rigoureuse que les hommes.

Mots-clés: infarctus aigu du myocarde – registre national – intervention coronaire – temps de transfert – différences liés au sexe

INTRODUCTION

L'infarctus aigu du myocarde (AMI) est une des causes principales de mortalité au Luxembourg à la fois pour les hommes et pour les femmes. L'AMI correspond à la destruction d'une partie plus ou mois importante du muscle cardiaque suite à l'oblitération par une thrombose (formation d'un caillot) d'une artère coronaire permettant habituellement l'irrigation (flux coronarien) du myocarde. Cette obstruction provoque un apport insuffisant de sang riche en oxygène et en nutriments et provoque la nécrose d'une partie du muscle cardiaque (31).

Le but du registre national LUCKY est l'évaluation des résultats obtenus avec les traitements mis en place chez les patients présentant un AMI et admis à l'INCCI pour une intervention percutanée coronarienne (PCI). **Le registre Lucky va fournir pour la première fois des données importantes sur le traitement de l'infarctus au Luxembourg.** Le registre fournit une observation des pratiques

réelles et ne peut pas se substituer aux études randomisées. Le registre Lucky permet entre autre de faire une comparaison entre la manière dont les hommes et femmes sont traités au Luxembourg.

La première cause de décès chez les femmes n'est pas le cancer du sein mais l'infarctus du myocarde, mais leur dépistage et leur prévention sont largement sous-estimés dans le monde médical.

Les maladies cardiovasculaires sont à l'origine du décès de 8,5 millions de femmes chaque année. C'est la première cause de mortalité féminine, représentant un tiers de tous les décès (3).

- les maladies cardiovasculaires touchent les femmes en moyenne 10 ans plus tard que les hommes, probablement à cause du rôle protecteur des estrogènes avant la ménopause (3);
- le tabagisme est l'un des facteurs de risque majeur pour les maladies cardiovasculaires et les AVC. Pour les femmes, le risque d'infarctus est multiplié par 1,7 en cas d'une consommation tabagique modérée (10 cigarettes/jour) et par 4 chez les grandes fumeuses (20 cigarettes/jour) (3-4);
- le tabagisme passif augmenterait le risque cardiovasculaire de 30% pour les femmes (9);
- l'association pilule cigarette (plus de 15 cigarettes par jour) multiplie par trois le risque cardiovasculaire (10).
- les femmes hypertendues ont un risque de maladies cardiovasculaires multiplié par 3,5 par rapport aux femmes dont la tension artérielle est normale (12);
- les femmes diabétiques ont un risque cardiovasculaire multiplié par 8 par rapport aux femmes non diabétiques (alors qu'il est seulement multiplié par 3 chez les hommes) (13);
- l'inactivité physique double le risque de développer une maladie cardiovasculaire et augmente le risque d'hypertension de 30%. Elle double également le risque de décès par maladies cardiovasculaires et AVC (15);
- l'obésité augmente le risque de mort prématurée due à des problèmes cardiovasculaires comme l'hypertension, les AVC, l'infarctus (25).

Rôle de l'œstrogène avant et après la ménopause

Avant la ménopause les estrogènes proviennent essentiellement de la sécrétion ovarienne, **après la ménopause** ils résultent de la transformation des androgènes surrénaliens sous l'influence de l'aromatase des tissus périphériques.

Jusqu'à la ménopause, les femmes sont plus «protégées» des accidents cardiovasculaires grâce à leurs estrogènes, mais après cette date leur risque de mourir d'un accident coronarien rattrape celui des hommes. Cela s'explique par l'effet des

œstrogènes sur le profil lipidique beaucoup plus favorable que celui des hommes avec:

- un taux de cholestérol total plus bas;
- une concentration moins forte du niveau des triglycérides;
- une teneur en HDL-cholestérol plus élevée.

Ce phénomène explique en partie pourquoi la fréquence des maladies cardiovasculaires est très faible chez les femmes avant 50 ans et en tout cas bien plus basse que chez les hommes.

Le taux de cholestérol total s'accroît de 6 à 9% après la ménopause tandis que celui du LDL-cholestérol augmente de 10 à 16% et que la concentration des triglycérides s'élève, en moyenne de 11%. Ainsi, le niveau de cholestérol moyen, qui était inférieur à celui relevé chez les hommes avant 50 ans, va le dépasser après 55 ans. Par ailleurs, le taux de HDL-cholestérol diminue de 10% environ dans les années qui précèdent la ménopause (17). Ces changements lipidiques participent tous à une augmentation du risque d'athérosclérose. Ils contribuent à majorer l'apparition des maladies cardiovasculaires, qui deviendront aussi fréquentes chez les femmes que chez les hommes vers 80 ans.

D'autres facteurs interviennent vers l'âge de 50 ans comme:

- -la prise de poids;
- -une modification de la répartition des graisses du corps;
- -une élévation de la pression artérielle;
- -une tendance à présenter un excès de glucose dans le sang.

En dehors de l'effet sur le métabolisme des lipides, les œstrogènes ont, par ailleurs, des effets directs sur la paroi artérielle (vasodilatation, sécrétion de PGI2, de NO...). Ces effets jouent sans doute un rôle majeur sur l'altération du lit artériel après la ménopause, mais ce rôle n'a pas été spécifiquement étudié, contrairement aux modifications du métabolisme lipidique, dans de grandes études longitudinales. Cependant, l'hypertrophie ventriculaire gauche constatée à l'échographie après la ménopause est sans doute la conséquence de la diminution de la compliance artérielle et donc l'augmentation de la pression artérielle (14).

Autres facteurs de risques qui interviennent avant la ménopause

Le risque d'infarctus du myocarde augmente proportionnellement avec le nombre de facteurs de risque cumulés pour une femme: cholestérol élevé, hypertension artérielle, tabagisme, diabète, obésité abdominale, stress, consommation d'alcool.

Le tabagisme est celui dont la prévalence a le plus évolué chez la femme au cours de ces trois dernières décennies. Ce tabagisme débute tôt dans l'adolescence et

persiste plus que chez les hommes à l'âge adulte. Entre 1980 et 2000, le nombre de fumeurs âgés de plus de 15 ans a diminué de 45% à 33% chez les hommes alors qu'il est passé de 17% à 21% chez les femmes et continue à augmenter dans toutes les tranches d'âge. Il est devenu le facteur de risque dominant de la femme non ménopausée (16). La protection relative liée à son statut hormonal, dont elle bénéficie jusqu'à la ménopause, ne la met pas à l'abri des dangers du tabagisme. La consommation de cigarettes est à l'origine d'au moins 50% des accidents coronaires survenant entre 30 et 55 ans. Le nombre de cigarettes fumées est corrélé positivement avec le risque de décès par maladie coronaire, avec le risque d'infarctus du myocarde et avec le risque d'accident vasculaire cérébral. Il existe un effet synergique très important de l'association d'un tabagisme avec d'autres facteurs de risque. L'association tabagisme et contraception estroprogestative augmente de façon significative le risque d'infarctus du myocarde et d'accident vasculaire cérébral. Les mécanismes des complications cardiovasculaires liées au tabagisme, en particulier le spasme et la thrombose, expliquent la possibilité d'accidents chez les sujets relativement jeunes y compris en l'absence de lésions artérielles visibles. Ces mécanismes sont activés pour des niveaux très faibles d'exposition. Il n'y a pas de seuil de consommation au dessous duquel il n'y a aucune augmentation du risque cardiovasculaire. La nicotine est essentiellement responsable de la dépendance vis-à-vis du tabac, mais ne semble pas en cause dans la toxicité cardiovasculaire. Si le monoxyde de carbone est assurément un élément très délétère chez les patients coronariens, c'est le rôle des radicaux libres, responsables d'une augmentation du «stress oxydatif», qui est surtout mis en avant dans la constitution des lésions artérielles et la survenue des accidents cardiovasculaires.

Une autre **différence importante entre le cœur d'un homme et d'une femme réside dans le fait que ce dernier est plus petit** (26). Les artères et les veines ont un diamètre inférieur (27). Il est possible que ces vaisseaux soient plus sensibles à l'obstruction.

Inégalités dans le diagnostic et la prise en charge (20-24; 28,29).

Les symptômes de l'infarctus chez les hommes sont décrits avec précision, les symptômes observables chez les femmes sont trop souvent méconnus. Chez les hommes l'accident coronarien aigu est relativement facile à reconnaître (forte douleur à la poitrine et au bras gauche), chez les femmes les symptômes sont plutôt vagues.

Moins bien diagnostiquées que les hommes à cause d'une idée fausse comme quoi les maladies cardiovasculaires sont «des maladies masculines». Cette idée fausse conduit à une sous-estimation de la gravité des symptômes et retarde une intervention rapide chez les femmes. Les symptômes classiques sont moins souvent présents chez les femmes.

Les femmes sont moins bien prises en charge que les hommes. L'étude Euro Heart Survey réalisée en 2003 auprès de 3779 patients se plaignant de douleurs

thoraciques à travers 36 pays, montre à quel point les femmes ne sont pas les égales des hommes devant les maladies cardiovasculaires. Elles ont 20% de moins de chances qu'un homme de se voir prescrire un test d'effort, qui reste pourtant une épreuve permettant de confirmer le diagnostic et de déterminer le traitement nécessaire. Elles ont 40% de moins de chances qu'un homme d'avoir une angiographie coronaire, un autre examen déterminant la présence et l'extension de l'obstruction des artères coronaires. Les femmes diagnostiquées avec un angor instable recevaient moins fréquemment que les hommes un traitement de long terme avec de l'aspirine (73% contre 84%) ou un hypolipémiant comme les statines (47% contre 53%). Plus alarmant encore, après une année de suivi, ces femmes étaient plus nombreuses que les hommes à être victimes d'une attaque cardiaque ou décès dus à une complication.

Le but de notre étude était d'analyser la prise en charge des femmes avec infarctus au Luxembourg.

MATERIELS ET METHODES

Schéma d'étude

Il s'agit du registre d'un seul centre d'observation du Luxembourg, l'INCCI.

Une majorité de patients avec infarctus aigu du myocarde sont transférés à l'INCCI.

Le registre a débuté en Février 2006.

Population

Les patients avec AMI sont admis au centre de cathétérisme cardiaque de l'INCCI pour intervention coronarienne en urgence. Le AMI est défini par une douleur thoracique typique de la poitrine < 12 heures et la présence d'élévation significative du segment ST trouvé sur au moins 2 dérivations de l'ECG. Tous les patients sont informés et signent un consentement.

Recueil et nature des données

Les données nécessaires à l'étude ont été recueillies sur la base d'un questionnaire, à partir des sources d'information suivantes : examen clinique du patient, compte-rendu d'hospitalisation, entretien éventuel avec le médecin de famille désigné par le patient en cas des données manquantes ou incomplètes. Les principales informations recherchées étaient :

- l'existence de facteurs de risque cardiovasculaire ou antécédents:
  - Hypertension artérielle (pression artérielle systolique>140mmHg et pression artérielle diastolique>90mmHg)

- Surcharge pondérale: lors de l'examen clinique du malade, elle était estimée par le calcul de l'indice de masse corporelle(BMI), défini par le rapport poids (kg)/surface corporelle (m^2).Le surpoids était défini par un BMI>25, selon la classification de l'Organisation mondiale de la santé (OMS).
- Hypercholestérolémie (LDL-cholestérol > 1,3g/l).
- Diabète
- Tabagisme
- Familiaux.

- médication avant intervention.
- médication pendant intervention.
- médication après intervention.
- délais entre le début de la douleur thoracique et le premier contact.
- délais entre le début de la douleur thoracique et l'arrivée a l'INCCI.
- délais entre le premier contact et l'arrivé a l'INCCI.
- complications après 1mois.
- fraction d'éjection déterminée par échocardiographie à 1 mois.

La base de données est localisée dans le système COPRA utilise à l'INCCI pour suivre les données des patients pour les interventions percutanées.

Patients non considérés et données manquantes

Les données manquantes des patients non considérés ne sont pas remplacées.

Les dates et les temps absents ne sont pas remplacés.

Méthodes statistiques

Les intervalles de temps ont été analysés avec le modèle de risques proportionnels de Cox en intégrant les caractéristiques de patients, les facteurs de risque, l'état clinique et les traitements précédents indiqués.

Un modèle de régression logique a été utilisé pour évaluer l'association de la fraction d'éjection (≤40%, >40%) après 1 mois de suivi avec les caractéristiques des patients, la stratégie de traitement et les résultats des tests biologiques.

La modélisation a procédé par élimination descendante pas à pas, nécessitant un $p < 0.05$ pour être significatif, et en commençant par un modèle qui comporte toutes les variables (modèle saturé). Les interactions entre les variables ont été testées suivant la même méthode. Les variables significatives cliniquement ont été forcées dans le modèle. Le test de Chi carré et le test de vraisemblance ont été utilisés pour mesurer l'importance des variables dans le modèle.

Le modèle linéaire général a été utilisés pour étudier la relation entre les variables continues (fraction d'éjection,…) et les caractéristiques des patients.

Une valeur de $p<0.05$ était considérée comme significative. Tous les tests effectués étaient bilatéraux. Les analyses ont été effectuées avec le logiciel SAS System version 9.1.3 (SAS Institute, Cary, NC).

RESULTATS

Critères généraux, antécédents et traitements médicamenteux avant l'infarctus

Un total de 153 patients consécutifs (112 hommes et 41 femmes) qui présentaient un infarctus aigu et qui ont subi une intervention coronaire à l'INCCI a été inclus dans cette étude. On constate chez les femmes admises pour infarctus quelques différences générales statistiquement significatives ($p<0,001$) par rapport aux hommes (fig.1a). Elles sont plus jeunes que les hommes quand elles font un infarctus (moyenne de 60 ans contre 62 ans chez les hommes). Leur poids est plus élevé par rapport aux hommes (moyenne de 85 kg contre 80 kg chez les hommes). Leur taille est plus élevée par rapport aux hommes (moyenne de 173 cm contre 170 cm chez les hommes). Elles ont un BMI plus important par rapport aux hommes (moyenne de 28 contre 27 chez les hommes).

Les antécédents médicaux ne montrent pas de différences significatives entre les hommes et les femmes, en particulier concernant les facteurs de risque cardiovasculaire. Il y a une tendance chez les hommes à fumer d'avantage (fig.2a).

Il n'y a pas de différence significative, en ce qui concerne les délais. En effet, les 3 délais de prise en charge sont équivalents entre les hommes et les femmes. On note que bien que la moitié des patients contacte le système de santé pendant la première heure qui suit le début des douleurs, malheureusement presque la moitié arrive seulement après de longs délais à l'INCCI (fig.2a, fig.2b, fig.2c).

Les femmes reçoivent statistiquement ($p<0,01$) moins de statines que les hommes (tableau 1) avant l'intervention, malgré une tendance à présenter un cholestérol plus élevé (fig.3 et tab. 2).

Déroulement de l'intervention

Une moindre administration du REOPRO, un inhibiteur puissant des récepteurs GPIIb/IIIa sur les plaquettes (3-6), est observée pour l'ensemble des patients d'un âge avancé ($p=0,015$).

On constate aussi que l'ensemble des hommes reçoivent en moyenne presque 2 fois plus de Reopro que les femmes (60% contre 35%) pendant l'intervention (fig.4).

Suivi à un mois

Les statines sont significativement ($p<0.04$) moins administrées aux femmes au décours immédiat de l'intervention (tab.3). Elles reçoivent également mois de ß-bloquants (tab.3 et fig.6). On constate au niveau des statines, une sous- médication significative ($p<0.01$) chez les femmes après l'infarctus (tab.4 et fig.5).

Il est important de noter qu'un tiers des patients présentent une dysfonction sévère du ventricule gauche (FE<30%) après infarctus. Ces patients ont un risque important de développer une insuffisance cardiaque. Il n'y a pas de différence entre hommes et femmes en ce qui concerne la fraction d'éjection du ventricule gauche après infarctus (Fig.7).

Les décès sont rares et témoignent d'une bonne prise en charge d'une maladie grave. De même, les ré-infarctus sont peu fréquents. Un certain nombre des patients doit subir une ré-intervention sur une autre artère coronaire pendant la même hospitalisation (fig.8).

DISCUSSION

Les résultats les plus importants de cette analyse sont qu'il y a bien une différence de prise en charge entre les hommes et les femmes avant et après infarctus.

1. Les femmes ont un BMI plus important.

Dans la littérature, le BMI est corrélé au risque de survenue d'infarctus du myocarde, au taux de mortalité par infarctus du myocarde et également au risque de récidive d'infarctus du myocarde. Le poids étant un facteur de risque modifiable, il convient d'insister sur la surveillance de ce paramètre et d'éduquer les patients.

2. Les femmes reçoivent moins de statines que les hommes.

En prévention primaire l'instauration d'un traitement par une statine devrait être considéré à partir d'un taux cible de LDL- cholestérol à 1,3g/l si plusieurs essais de régime alimentaire, tous basés sur une diminution des apports en acides gras saturés ou en graisses animales, n'ont pas eu de résultats.

Trois grands essais cliniques, en prévention secondaire chez des patients ayant des antécédents d'infarctus du myocarde, ont confirmé que les statines réduisent le risque de récidive et la mortalité.

Dans notre étude, nous avons observé que sur 16 femmes présentant une hypercholestérolémie avant l'infarctus du myocarde, 2 femmes seulement ont bénéficié d'un traitement par une statine. Un mois après l'intervention seulement 24 femmes (sur 43) ont reçu un traitement par une statine, par rapport à 94 hommes (sur 118).

3. Délais entre début d'une douleur thoracique et arrivée à l'INCCI.

Le pronostic des patients victimes d'un infarctus aigu du myocarde est lié à l'étendue de la nécrose et à l'altération de la fonction ventriculaire. En l'absence de circulation collatérale, la proportion de myocarde épargné au sein de la zone à risque dépend de la rapidité de la restauration d'une perfusion adéquate. Il est essentiel de réduire au minium la durée de l'occlusion coronaire. Idéalement, le temps qui s'écoule entre l'occlusion d'une artère et la reperfusion du muscle cardiaque ne doit pas excéder deux heures. Au-delà, le risque de complication est accru.

Il semble donc se confirmer la nécessité d'une information grand public et ciblée sur la douleur thoracique (DT). De plus, des messages rappelant la nécessité d'un appel précoce aux services d'urgence quand la DT apparaît sont nécessaires. La collaboration entre les différents acteurs (généraliste, policlinique, cardiologue, SAMU) pourra encore être améliorée notamment avec des moyens de télémédecine.

En conclusion, l'angioplastie primaire a pu réduire de manière spectaculaire la morbidité, mortalité de l'infarctus aigu. Le registre national Lucky confirme ceci pour le Luxembourg. Cependant, un tiers des patients garde une dysfonction sévère après infarctus. Il est possible que ce pourcentage puisse être diminué par une prise en charge plus rapide du patient. En ce qui concerne les femmes, il faut insister sur le fait qu'elles ne sont pas épargnées par l'infarctus et qu'il faut les traiter de manière aussi rigoureuse que les hommes.

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CONFLITS D'INTERET

Les auteurs ne déclarent aucun conflit d'intérêt.

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FIGURES:

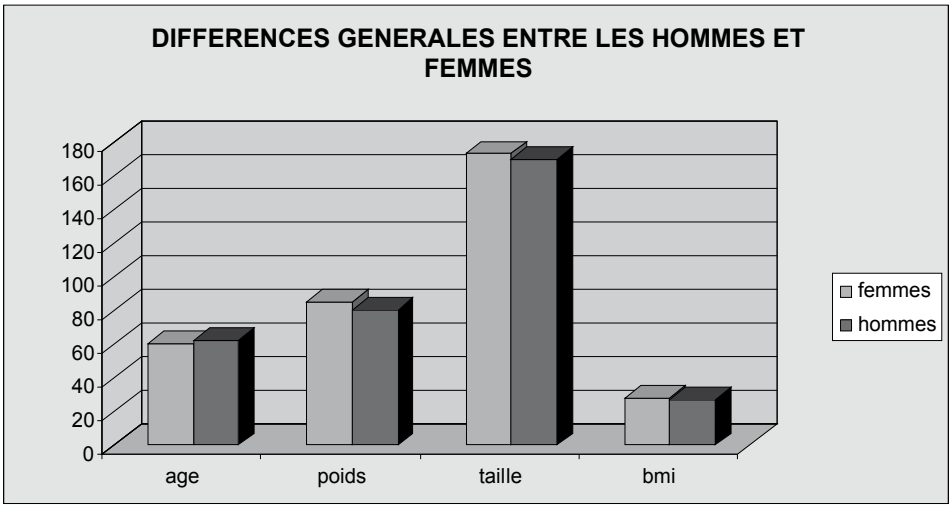


Fig.1a: montre les caractéristiques cliniques des patients.

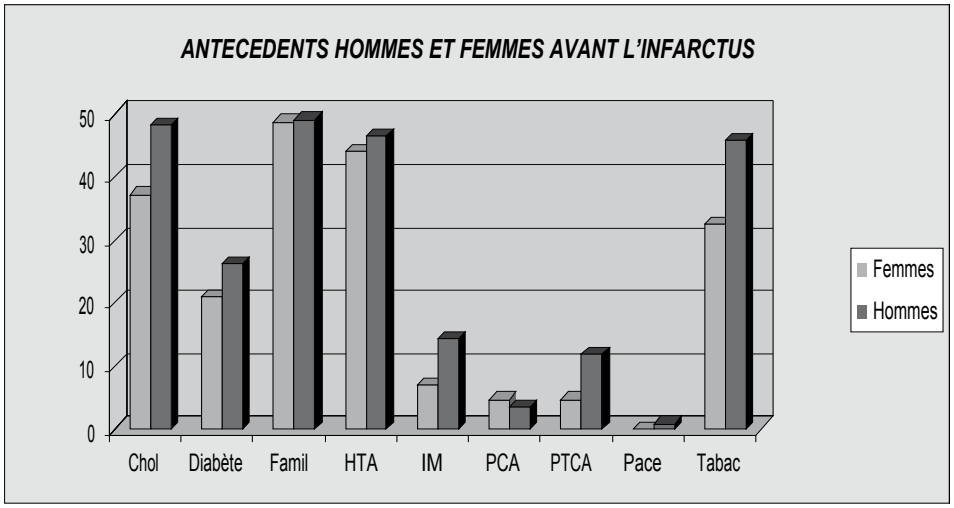


Fig.1b: montre les antécédents cliniques des patients.

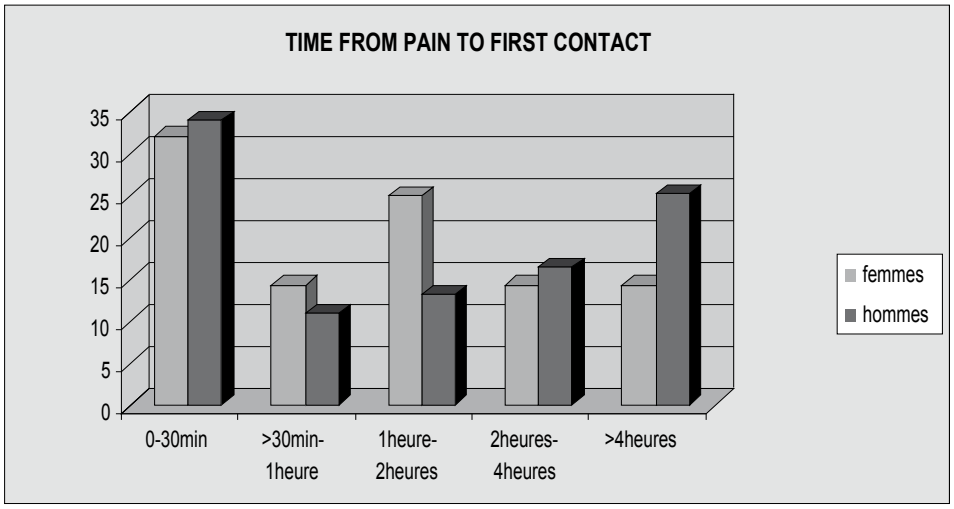


Fig.2a: montre le délai entre le début de la douleur thoracique et le premier contact.

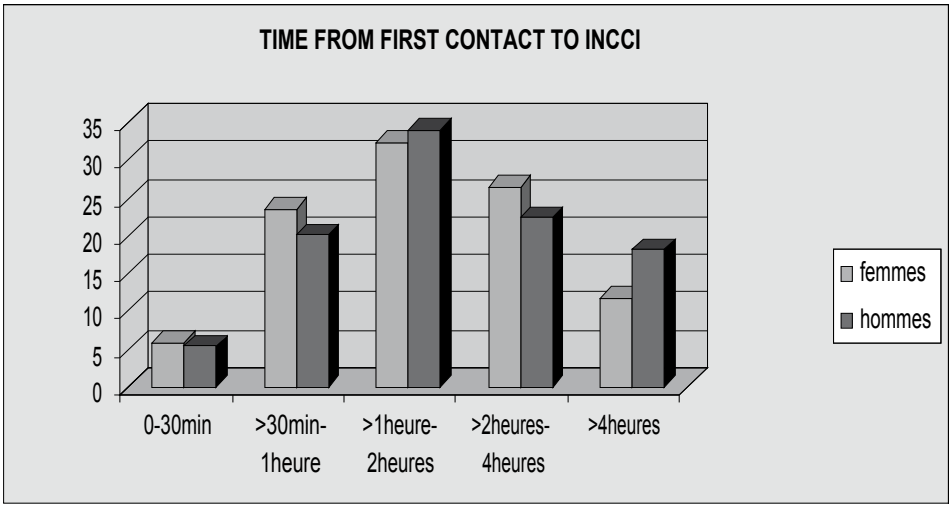


Fig.2b: montre le délai entre le premier contact et l'arrivé à l'INCCI.

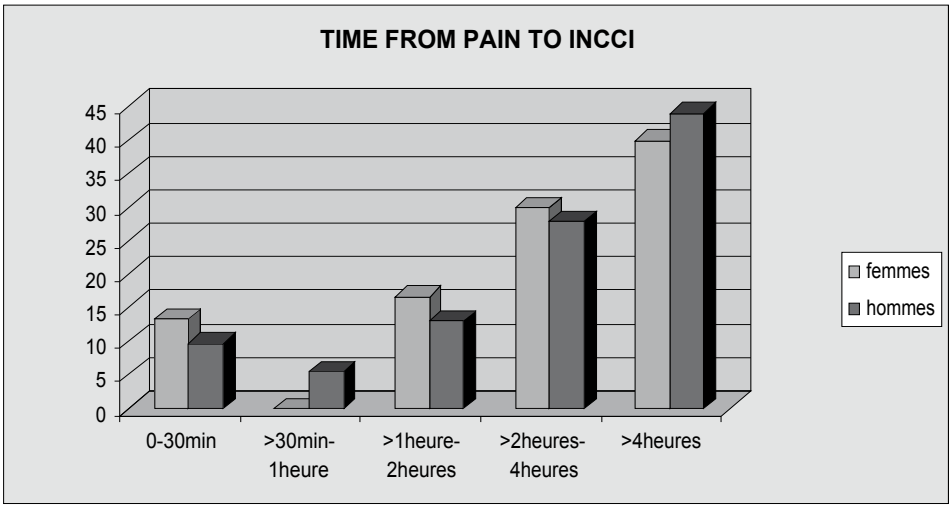


Fig.2c: montre le délai entre le début de la douleur thoracique et l'arrivé à l'INCCI.

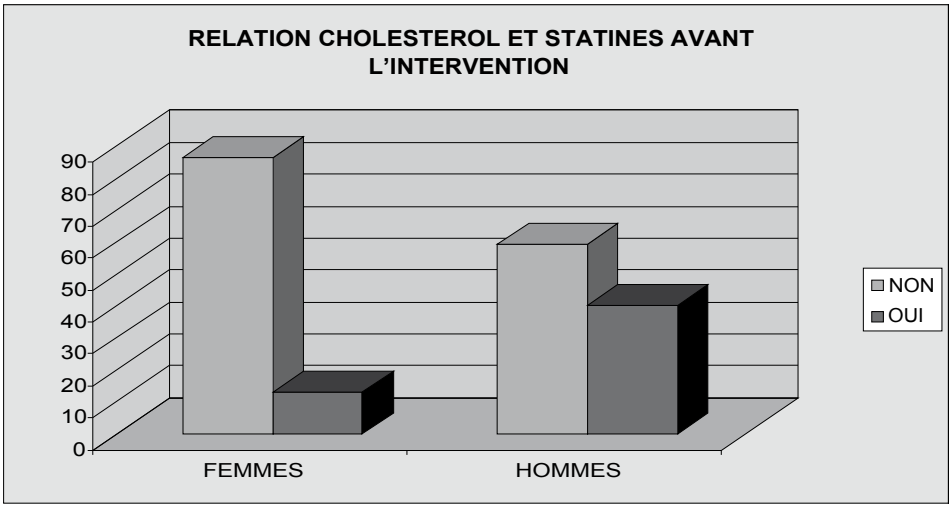


Fig.3: montre la relation entre le cholestérol et les statines avant l'intervention.

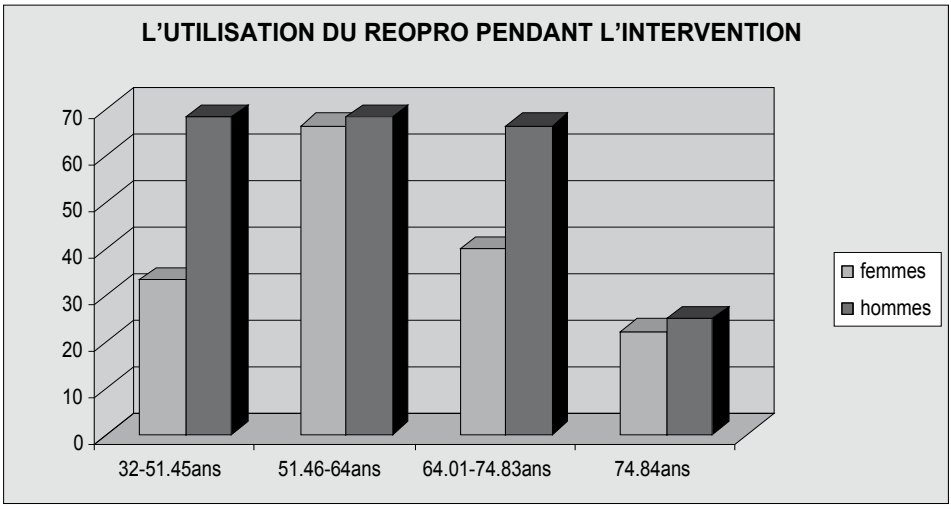


Fig.4: montre l'utilisation du REOPRO pendant l'intervention.

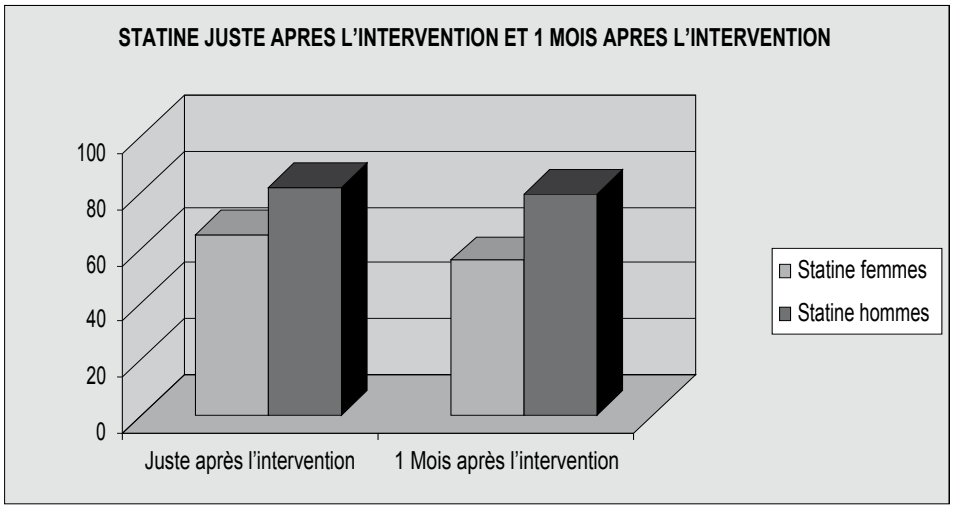


Fig.5: montre l'administration de statine juste après l'intervention et 1mois après l'intervention.

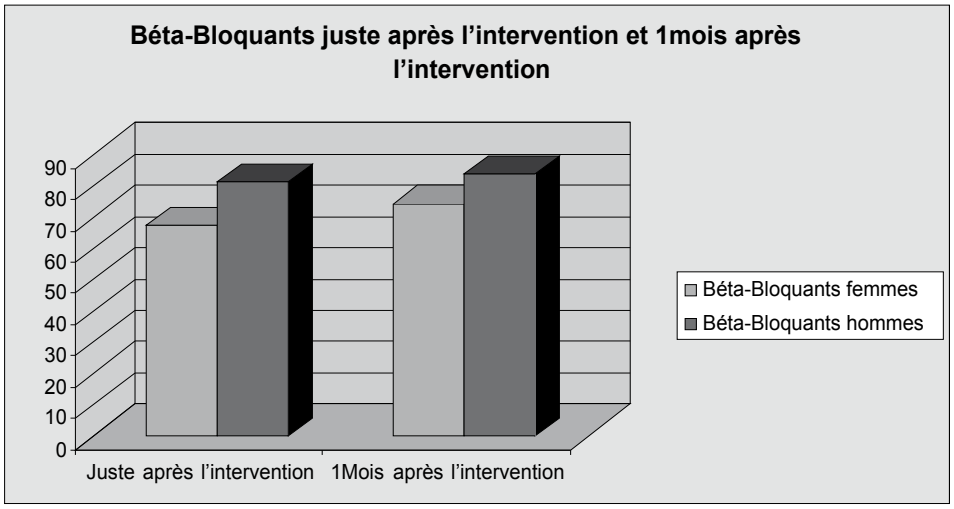


Fig.6: montre l'administration de béta-bloquants juste après l'intervention et 1mois après l'intervention.

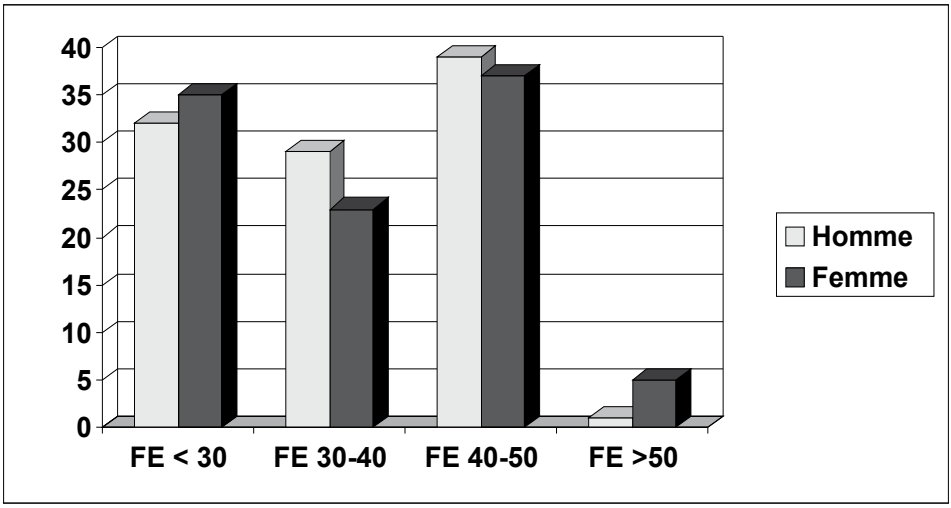


Fig.7: montre les résultats écho cardiographique à 1mois.

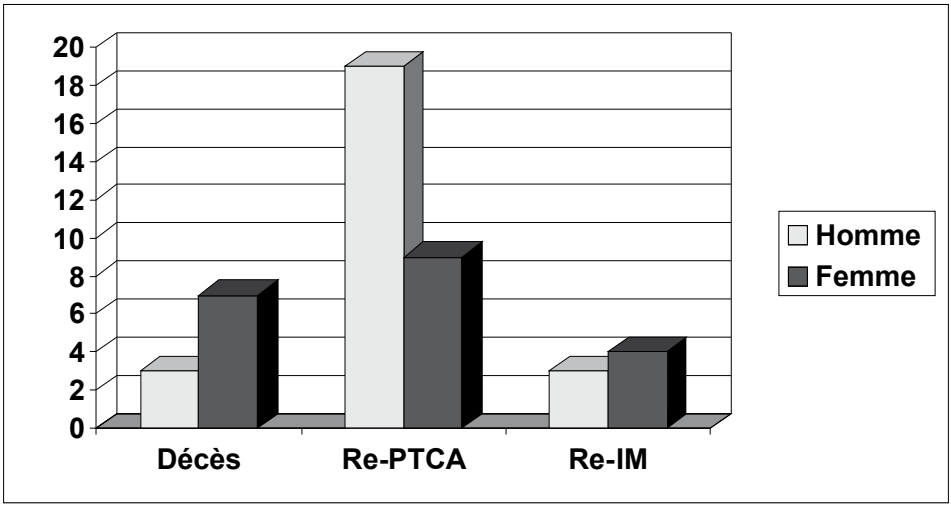


Fig.8: montre les complications à 1mois.

Tab.1: montre la médication des patients avant l'intervention.

		Féminin		Masculin		TOTAL		Chi2 p-value
Variable	**Classes**	**N**	**%**	**N**	**%**	**N**	**%**	
AII	**Oui**	1	2.33	6	5.08	7	4.35	0.46
	Non	41	95.35	112	94.92	153	95.03	
	Inconnu	1	2.33	.	.	1	0.62	
Aspirine	**Oui**	39	90.70	115	97.46	154	95.65	0.18
	Non	3	6.98	3	2.54	6	3.73	
	Inconnu	1	2.33	.	.	1	0.62	
Béta-Bloquants	**Oui**	29	67.44	96	81.36	125	77.64	0.10
	Non	13	30.23	22	18.64	35	21.74	
	Inconnu	1	2.33	.	.	1	0.62	
Ca2	**Oui**	1	2.33	2	1.69	3	1.86	0.78
	Non	41	95.35	116	98.31	157	97.52	
	Inconnu	1	2.33	.	.	1	0.62	
Cordarone	**Oui**	2	4.65	5	4.24	7	4.35	0.89
	Non	40	93.02	113	95.76	153	95.03	
	Inconnu	1	2.33	.	.	1	0.62	
Diurétiques	**Oui**	5	11.63	12	10.17	17	10.56	0.75
	Non	37	86.05	106	89.83	143	88.82	
	Inconnu	1	2.33	.	.	1	0.62	
Fibrates	**Oui**	.	.	.	.	.	.	0.78
	Non	42	97.67	118	100.00	160	99.38	
	Inconnu	1	2.33	.	.	1	0.62	
Héparine	**Oui**	42	97.67	115	97.46	157	97.52	0.30
	Non	.	.	3	2.54	3	1.86	
	Inconnu	1	2.33	.	.	1	0.62	
IEC	**Oui**	15	34.88	52	44.07	67	41.61	0.33
	Non	27	62.79	65	55.08	92	57.14	
	Inconnu	1	2.33	1	0.85	2	1.24	
Nitro	**Oui**	7	16.28	32	27.12	39	24.22	0.18
	Non	35	81.40	86	72.88	121	75.16	
	Inconnu	1	2.33	.	.	1	0.62	
Plavix	**Oui**	41	95.35	115	97.46	156	96.89	0.95
	Non	1	2.33	3	2.54	4	2.48	
	Inconnu	1	2.33	.	.	1	0.62	
Réopro	**Oui**	19	44.19	71	60.17	90	55.90	0.09
	Non	23	53.49	47	39.83	70	43.48	
	Inconnu	1	2.33	.	.	1	0.62	
Sintrom	**Oui**	.	.	1	0.85	1	0.62	0.55
	Non	42	97.67	117	99.15	159	98.76	
	Inconnu	1	2.33	.	.	1	0.62	
Statines	**Oui**	28	65.12	97	82.20	125	77.64	0.04
	Non	14	32.56	21	17.80	35	21.74	
	Inconnu	1	2.33	.	.	1	0.62	

Tab.2: montre la relation entre le cholestérol et la statine avant l'intervention.

	Female			**Male**			**ALL**		
cholesterol	**Statine**			**Statine**			**Statine**		**Total**
Frequency **Col Pct**	**Non**	**Oui**	**Total**	**Non**	**Oui**	**Total**	**Non**	**Oui**	
Non	26 66.7	0 0	26	54 61.4	6 20.7	60	80 63	6 19.4	86
Oui	13 33.3	2 100	15	34 38.6	23 79.3	57	47 37	25 80.7	72
Total	39 95.1	2 4.9	41 100	88 75.2	29 24.8	117 100	127 80.4	31 19.6	158 100
	Missing = 2, p-value=0.13			**Missing = 1, p-value<0.001**			**Missing = 3, p-value<0.001**		

Tab.3: montre la médication des patients pendant l'intervention.

		Féminin		Masculin		TOTAL		Chi2 p-value
Variable	**Classes**	**N**	**%**	**N**	**%**	**N**	**%**	
AII	**Oui**	1	2.33	6	5.08	7	4.35	0.46
	Non	41	95.35	112	94.92	153	95.03	
	Inconnu	1	2.33	.	.	1	0.62	
Aspirine	**Oui**	39	90.70	115	97.46	154	95.65	0.18
	Non	3	6.98	3	2.54	6	3.73	
	Inconnu	1	2.33	.	.	1	0.62	
Béta-Bloquants	**Oui**	29	67.44	96	81.36	125	77.64	0.10
	Non	13	30.23	22	18.64	35	21.74	
	Inconnu	1	2.33	.	.	1	0.62	
Ca2	**Oui**	1	2.33	2	1.69	3	1.86	0.78
	Non	41	95.35	116	98.31	157	97.52	
	Inconnu	1	2.33	.	.	1	0.62	
Cordarone	**Oui**	2	4.65	5	4.24	7	4.35	0.89
	Non	40	93.02	113	95.76	153	95.03	
	Inconnu	1	2.33	.	.	1	0.62	
Diurétiques	**Oui**	5	11.63	12	10.17	17	10.56	0.75
	Non	37	86.05	106	89.83	143	88.82	
	Inconnu	1	2.33	.	.	1	0.62	
Fibrates	**Oui**	.	.	.	.	.	.	0.78
	Non	42	97.67	118	100.00	160	99.38	
	Inconnu	1	2.33	.	.	1	0.62	
Héparine	**Oui**	42	97.67	115	97.46	157	97.52	0.30
	Non	.	.	3	2.54	3	1.86	
	Inconnu	1	2.33	.	.	1	0.62	
IEC	**Oui**	15	34.88	52	44.07	67	41.61	0.33
	Non	27	62.79	65	55.08	92	57.14	
	Inconnu	1	2.33	1	0.85	2	1.24	
Nitro	**Oui**	7	16.28	32	27.12	39	24.22	0.18
	Non	35	81.40	86	72.88	121	75.16	
	Inconnu	1	2.33	.	.	1	0.62	
Plavix	**Oui**	41	95.35	115	97.46	156	96.89	0.95
	Non	1	2.33	3	2.54	4	2.48	
	Inconnu	1	2.33	.	.	1	0.62	
Réopro	**Oui**	19	44.19	71	60.17	90	55.90	0.09
	Non	23	53.49	47	39.83	70	43.48	
	Inconnu	1	2.33	.	.	1	0.62	
Sintrom	**Oui**	.	.	1	0.85	1	0.62	0.55
	Non	42	97.67	117	99.15	159	98.76	
	Inconnu	1	2.33	.	.	1	0.62	
Statines	**Oui**	28	65.12	97	82.20	125	77.64	0.04
	Non	14	32.56	21	17.80	35	21.74	
	Inconnu	1	2.33	.	.	1	0.62	

Tab.4: montre la médication des patients 1mois après l'intervention.

		Féminin		Masculin		TOTAL		Chi2 p-value
Variable	**Classes**	**N**	**%**	**N**	**%**	**N**	**%**	
AII	**Oui**	4	9.30	5	4.24	9	5.59	0.20
	Non	35	81.40	104	88.14	139	86.34	
	Inconnu	4	9.30	9	7.63	13	8.07	
Aldactone	**Oui**	1	2.33	.	.	1	0.62	0.09
	Non	38	88.37	109	92.37	147	91.30	
	Inconnu	4	9.30	9	7.63	13	8.07	
Aspirine	**Oui**	37	86.05	104	88.14	141	87.58	0.89
	Non	2	4.65	5	4.24	7	4.35	
	Inconnu	4	9.30	9	7.63	13	8.07	
Béta-Bloquants	**Oui**	32	74.42	99	83.90	131	81.37	0.14
	Non	7	16.28	10	8.47	17	10.56	
	Inconnu	4	9.30	9	7.63	13	8.07	
Ca2	**Oui**	5	11.63	6	5.08	11	6.83	0.13
	Non	34	79.07	103	87.29	137	85.09	
	Inconnu	4	9.30	9	7.63	13	8.07	
Cordarone	**Oui**	3	6.98	5	4.24	8	4.97	0.46
	Non	36	83.72	104	88.14	140	86.96	
	Inconnu	4	9.30	9	7.63	13	8.07	
Diurétiques	**Oui**	11	25.58	18	15.25	29	18.01	0.11
	Non	28	65.12	91	77.12	119	73.91	
	Inconnu	4	9.30	9	7.63	13	8.07	
Fibrates	**Oui**	1	2.33	.	.	1	0.62	0.09
	Non	38	88.37	109	92.37	147	91.30	
	Inconnu	4	9.30	9	7.63	13	8.07	
Héparine	**Oui**	1	2.33	1	0.85	2	1.24	0.44
	Non	38	88.37	108	91.53	146	90.68	
	Inconnu	4	9.30	9	7.63	13	8.07	
IEC	**Oui**	23	53.49	75	63.56	98	60.87	0.27
	Non	16	37.21	34	28.81	50	31.06	
	Inconnu	4	9.30	9	7.63	13	8.07	
Nitro	**Oui**	6	13.95	13	11.02	19	11.80	0.58
	Non	33	76.74	96	81.36	129	80.12	
	Inconnu	4	9.30	9	7.63	13	8.07	
Plavix	**Oui**	39	90.70	108	91.53	147	91.30	0.55
	Non	.	.	1	0.85	1	0.62	
	Inconnu	4	9.30	9	7.63	13	8.07	
Réopro	**Oui**	.	.	.	.	.	.	0.09
	Non	39	90.70	109	92.37	148	91.93	
	Inconnu	4	9.30	9	7.63	13	8.07	
Sintrom	**Oui**	1	2.33	5	4.24	6	3.73	0.58
	Non	38	88.37	104	88.14	142	88.20	
	Inconnu	4	9.30	9	7.63	13	8.07	
Statines	**Oui**	24	55.81	94	79.66	118	73.29	<0.01
	Non	14	32.56	15	12.71	29	18.01	
	Inconnu	5	11.63	9	7.63	14	8.70	

Cinquantième anniversaire de la clinique neurologique de l'Inselspital de Berne

En tant que président de la SSM et membre de la Société Suisse de Neurophysiologie et par l'intermédiaire de notre membre d'honneur le Prof. K. Karbowski j'ai eu l'honneur et le plaisir d'être invité par le Prof. Christian Hess à un symposium international de haut niveau à l'Inselspital le 28 février 2008.

La première journée, destinée aussi aux généralistes, avait comme sujet: «*Neurologische Probleme im klinischen Alltag*» dont vous trouvez deux articles (avec l'autorisation de l'organisateur) ci-joints.

La deuxième journée, destinée aux spécialistes, traitait du sujet: «*Transcranial Magnetic Simulation in Clinical Diagnosis and Research*» avec notamment un remarquable exposé de A. Pascual-Leone de l'Université de Harvard: «*Understanding and Guiding Brain Plasticity with Noninvasiv Brain Stimulation*».

Le troisième jour fut consacré à «*Krankheiten des vegetativen Nervensystems*» où il faut relever la conférence de C.J. Mathias de Londres: «*Postural Tachycardial Syndrom, Past, Present and Future*».

Au dîner jubilaire à l'Hôtel Bellevue, le professeur Marco Mummenthaler, âgé de 83 ans, qui avait été pendant de longues années le professeur titulaire de la chaire de Neurologie à l'Inselspital, a fait un discours plein d'esprit et de verve sur l'histoire de la neurologie à Berne.

Henri Metz

Neurasthenie

Christian W. HESS

Neurologische Universitätsklinik, Inselspital, Ch-3010 Bern

Hypochondrie (auch: Melancholie) und Hysterie wurden von Ärzten seit dem Altertum gepflegt und können als Vorläufer der Neurasthenie aufgefasst werden. In der ersten Hälfte des 19. Jahrhunderts wurden Hypochondrie und Hysterie unter prägendem Einfluss des Franzosen Etienne-Jean Georget als Gehirnkrankheiten aufgefasst (Ostermeier 2005). Als „Chlorose" (Bleichsucht) wurde die chronische Blutungs-Anämie junger Frauen bezeichnet (Helfft, 1859), wobei sich manchmal psychische und psychosomatische Komponenten hineinmischten (Liebeskummer, Hysterie, Anorexie, etc.). Der Begriff der **Neurasthenie** als funktionelle Hirnkrankheit wurde im Jahre 1869 praktisch zeitgleich von zwei Amerikanern, dem Psychiater Edwin Van Deusen (Van Deusen 1869) und dem Neurologen George Miller Beard (Beard 1869) geprägt. Die Neurasthenie galt zuerst ais zivilisationsbedingte, typisch amerikanische „Nervosität", welche bald auf Europa hinüberschwappen sollte. Beard nahm wie viele andere auch eine vererbte Disposition an, was für das chronische Erschöpfungssyndrom heute als erwiesen gilt (Buchwald 2001).

Im Jahre 1975 unterschied George Poore erstmals zwischen zentraler (cerebraler) und peripherer (neuromuskulärer) Ermüdung (Poore 1875). Der italienische Physiologe Angelo Mosso untersuchte mittels Ergograph die periphere und zentrale Ermüdung systematisch, was er in seiner berühmten Monographie „La Fatica" 1891 publizierte. Der Berner Neurologieprofessor Paul Dubois replizierte diese Experimente, welche er in seiner berühmten Vorlesungsserie über Psychoneurosen publizierte (Dubois, 1910). Die Tatsache, dass nach ermüdungsbedingter sukzessiver Abnahme der wiederholten willkürlichen phasischen Kontraktionen diese durch elektrische Reizung des entsprechenden Nervs wieder deutlich grösser werden lassen konnten, gilt noch heute als Beweis der cerebralen Komponente der Ermüdung. Der Psychiater Kraepelin schliesslich führte 1901 die Unterscheidung zwischen „Ermüdung" und „Müdigkeit" ein (Kraepelin 1901).

In manchen alten Schilderungen der Syndrome oder der Patienten erkennt man unschwer das heutige chronische **Erschöpfungssyndrom** (chronic fatigue syndrome CFS, **Tabelle 2**) oder Intervall Fibromyalgiesyndrom (FMS), in welche die Neurasthenie mehrheitlich aufgegangen ist. Heute wird der Begriff Neurasthenie nach ICD-10 auf eine somatoforme Störung mit abnormer mentaler und physischer Ermüdbarkeit und Erschöpfung eingegrenzt (**Tabellen 3 & 4**) ohne klare Abgrenzung zum CSF, aber in der Psychiatrie nicht mehr allgemein verwendet. Die beiden modernen Etiketten CFS und FMS werden auch uneinheitlich gebraucht und haben einen grossen Überlappungsbereich von 20-70% (Afari et

Tabelle 2

2. Definition Neuroasthenie nach ICD-10 (F48.0)
folgenden Kriterien sind obligat:
• anhaltende und quälende Klagen über gesteigerte Ermüdbarkeit nach geistiger Anstrengung oder über körperliche Schwäche und Erschöpfung nach geringsten Anstrengungen
• Mindestens eines der folgenden Symptome:
- akute oder chronische Muskelschmerzen
- Benommenheit
- Spannungskopfschmerzen
- Schlafstörungen
- Unfähigkeit zu entspannen
- Reizbarkeit
• Die Betroffenen sind nicht in der Lage, sich durch Ruhe, Entspannung oder Ablenkung zu erholen.
• Dauer der Symptomatik mindestens 3 Monate

Anmerkungen: 1) Das Krankheitsbild tritt häufig im Anschluß an eine körperliche Erkrankung (z.B. Virusinfekt) oder nach besonderer Belastung durch Stress auf. 2) Die Diagnose existiert aber nicht im neuen Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) der Amerikanischen Psychiatrischen Vereinigung.

Tabelle 3

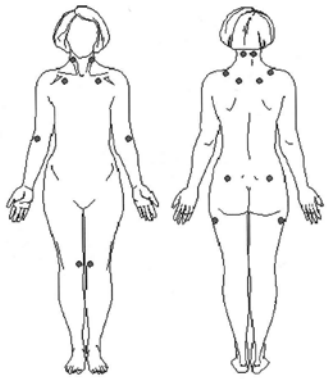
3. Definition des chronischen Erschöpfungssyndroms "chronic fatigue s." CFS (nach Fukuda 1994):
ausgeprägte physische und psychische Erschöpfbarkeit, ohne entsprechende vorherige Belastung, über einen längeren Zeitraum von ≥6 Monate, verbunden mit somato-psychischen Begleitsymptomen, Minderung der gewohnten sozialen und beruflichen Aktivitäten um >50%.
Zusätzlich mindestens 4 von 7 Neben-Kriterien:
- Halsweh
- schmerzhafte Lymphadenopathien cervikal oder axillär
- Myalgien
- überproportionale Ermüdung nach üblicher Belastung
- Arthralgien (ohne Rötung oder Schwellung)
- kognitive Einbussen wie Vergesslichkeit, Konzentrationsstörung
- Schlafstörung (z.B. nicht erfrischender Schlaf, Insomnie)

andere Definition: auch subfebrile Temperaturen, Reizbarkeit

Tabelle 4

4. Definition der Fibromyalgie (Wolfe 1990, Wysenbeek 1991)
• Eine nicht-entzündliche Erkrankung, die durch Schmerzen in der Muskulatur und in den Sehnenansätzen sowie durch eine erhöhte Druckempfindlichkeit an definierten Schmerzdruckpunkten gekennzeichnet ist. 18 Sehnenansätze bilden dieSchmerzdruckpunkte („Tender Points", Abbildung).
• Häufig assoziiert mit Schlafstörungen, Müdigkeit, Reizdarm, Kopfweh, Stimmungsschwankungen, Gedächtnis- & Konzentrationsstörungen, subfebrilen Temperaturenm und Gelenksschmerzen

Kriterien des The American College of Rheumatology (Wolfe 1990):
• Anamnese von ≥3 Mnt mit ausgedehnten Schmerzen, wie folgt lokalisiert:
- bilateral, oberhalb und unterhalb der Hüfte
- Achsel-Skelett (HWS oder Brustkorb oder Lumbago)
- Druckdolenz an 11 der 18 definierten Schmerzpunkte („Tender Points") am Nacken, Rücken, an den Schultern sowie an den Hüften (Abbildung)



al 2003, Wysenbeek 1991), so dass viele Autoren sie als dasselbe Syndrom betrachten. Die unklare Abtrennung kommt auch in der früher häufig gebrauchten Bezeichnung „myalgische Encephalomyelitis“ für CFS zum Ausdruck, welche zudem eine primär organische Ursache suggeriert. In der alten Literatur wurden unter Neurasthenie tatsachlich Syndrome beschrieben, welche heute auch andere, damals unbekannte internistische, neurologische und psychiatrische Krankheiten vermuten lassen (**Tabelle 1, siehe unten**). Je nach Symptomatik müssen diese zum grossen Teil somatischen Entitäten heute als Differentialdiagnose in Betracht gezogen werden.

Die Aetiologie des Komplexes Neurasthenie/CS/FMS ist immer noch ungeklärt. Seit den Anfängen bis heute wurde eine hauptsächlich **psychosomatische Genese** vertreten. Einigkeit besteht darüber, dass häufig zu starke „Schonung“ und Rückzug eine physische **Dekonditionierung** bewirkt, welche das Leiden auf verschiedenen Ebenen (Leistungsintoleranz, Schmerzen) verstärkt. Da die Beschwerden häufig nach einer akuten fieberhaften Erkrankung auftreten, wurde aber immer auch eine post- oder **parainfektiöse Ursache** vermutet, im 19. Jahrhundert v.a. Malaria, Influenza und Typhus, im letzten Jahrhundert Streptococcen, Enteroviren, Bruzellose, Gelbfieber, Schistosomiasis, St.Louis, Epstein-Barr, Cytomegalovirus, Varicella-Zoster-Virus, Cocksackie-B, Herpesvirus (HHV-6), Borrelien, HTL V-2, Rickettsien, Toxoplasmose und Impfungen (Rubella, Hepatitis-B), ohne dass die Aetiologie sich an grossen Patientenkollektiven erhärten liess (Wessely 1994). Da oft grippale Erkrankungen vorausgingen, war eine zeitlang auch der Begriff „postviral fatigue syndrome“ en vogue, wobei man im klinischen Alltag tatsächlich gelegentlich überzeugende postgrippale oder parainfektiöse Einzelfalle erlebt, bei welchen eine psychosomatische Ursache sehr unwahrscheinlich ist. Deshalb wird auch heute noch die Spur der erregerbedingten Fatigue intensiv verfolgt, und neuestens wurde eine persistierende Enterovireninfektion im Magen als mögliche Ursache identifiziert (Chia 2008).

Wegen der ähnlichen Phänomenologie wie die der Hypothyreose, wurde bei der Suche nach endokrinen Ursachen die Hypophysenachse analysiert. Bei einem Drittel der Patienten mit CFS wurde ein wahrscheinlich hypothalamischer leichter **Hypokortizismus** festgestellt (Parker 2001), was natürlich eine andere z.B. psychosomatische primäre Ursache nicht ausschliesst.

Bei der **Multiplen Sklerose** (MS) steht invalidisierende Müdigkeit häufig subjektiv ganz im Vordergrund, und sie kann sogar erst-präsentierendes Symptom sein. Konsequenterweise hat man bei der MS auto-immun entzündliche Mechanismen vermutet und nach Entzündungsmediatoren gesucht, welche für die Müdigkeit verantwortlich sein können. Tatsächlich sind die **Zytokine** TNF-α und IFN-γ bei MS Patienten mit Müdigkeit im Schnitt höher als bei solchen ohne Müdigkeit (Heesen 2005), was die parainfektiöse Hypothese auch bei CFS als Möglichkeit stützt. Als Kandidat wurde auch das Interleukin-6 studiert, das z.B. bei Athleten, wenn systemisch appliziert, die Leistungsfahigkeit beeinträchtigt (Robson-Ansley 2004) und auch die Hypophysenachse beeinflusst.

Einleuchtend sind auch Beschreibungen von schwer Schlaf-gestörten Patienten mit Müdigkeit und reduzierter Leistungsfähigkeit. Polysomnographisch konnte bei CFS und FMS ein typisches (aber nicht spezifisches) Alpha-Delta-Schlaf-Muster identifiziert werden, dessen pathogenetische Rolle aber unklar bleibt. Sicher muss aber ein **Schlaf-Apnoe-Syndrom** bei entsprechenden anamnestischen Verdachtsmomenten erwogen werden.

Mit einer viel beachteten Lancet-Publikation 1995 brachte der Pädiater Rowe aus Baltimore ein wichtiges neues Element in die Diskussion der Pathogenese: Er konnte mittels Kipptischuntersuchung bei 7 CFS-Patienten eine **orthostatische Hypotonie** nachweisen (Rowe 1995). Seither wird die **vegetative Dysautonomie,** welche auch postinfektiös auftreten kann, als mögliche Pathogenese verfolgt (Newton 2007). Weitere apparative Untersuchungen konnten die Befunde aber nur bei einem Teil der CFS Patienten replizieren. Die **orthostatische Intoleranz** mit Schwindel und Tachykardie (Schöndorf 1993), das sogenannte posturale Tachykardie-Syndrom (POTS), verursacht nicht obligat Synkopen und kann CFS-ähnliche Beschwerden verursachen **(Tabelle 6**).

Tabelle 6

6. Symptome und Befunde bei autonomer Polyneuropathie und Posturalem Tachykardiesyndrom (PoTS) (nach Kanjiwal 2003)

Symptome / Parameter	autonome Polyneuropathie	PoTS
Orthostatischer Schwindel	unterschiedlich	vorhanden (Hauptbeschwerden)
Orthostatische Zittrigkeit	keine	häufig
Orthostatische Palpitationen	keine	häufig
Ortostatische arterielle Hypotonie	konstant vorhanden	meist fehlend
Orthostatische Tachykardie	vermindert	verstärkt
Herzfrequenzanstieg nach Aufstehen*)	<10/min	≥30/min
Herzfrequenzvariabilität beim Atmen	vermindert	normal
S-Noradrenalin im Liegen	meist vermindert	normal oder erhöht
S-Noradrenalin im Stehen	vermindert	normal oder erhöht

*) 10 Minuten nach dem Aufstehen

Wir müssen davon ausgehen, dass Aetiologie und Pathogenese von Asthenie/ CFS/FMS **uneinheitlich** und z.T. wohl auch **multifaktoriell** sind (Afari 2003), weshalb es unser Ziel als „Somatiker“ sein muss, in diesem heterogenen Sammeltopf spezifische und somatisch behandelbare Formen zu identifizieren. Das beginnt schon mit der genauen Anamnese und klinischen Untersuchung.

Dabei sind folgende Punkte zu beachten.

- Unterscheidung müde versus deprimiert
  - müde schläfrig
  - Müdigkeit vorzeitige Ermüdbarkeit (=Leistungsintoleranz)
  - mentale physische Leistungsintoleranz
  - allgemeine muskuläre physische Leistungsintoleranz

• Schlafqualität und Schlafgewohnheiten (Schnarchen?)
• orthostatische Intoleranz - Parasynkopen?

Weiter muss sorgfältig nach assoziierten Beschwerden und Befunden gefahndet werden, um je nach Begleitsymptomen die unter **Tabelle 1** aufgelisteten Krankheiten zu suchen, welche einer kausalen Therapie zugänglich sind.

Tabelle 5

5. Minimales Labor bei Neurasthenie/CSF/FMS Beschwerden (nach Fukuda 1994):
Hb, Lc diff
BSR CRP
Niere (Kreatinin), Leber (ALAT = GPT), Glucose, Elektrolyte (Na, K, Ca, Phosphat), Cholesterin, Eiweiss, Harnstoff
Schilddrüsenfunktion (TSH)
ANA, Rheumafaktor
Urinstatus

Im Falle eines „reinen" CFS oder FMS sind die durch Studien belegten **Behandlungsoptionen** limitiert. Beim FMS wirken manchmal abendliche niedrig dosierte Antidepressiva gegen Schmerzen und Einschlafinsomnie (z.B. 10-30 mg Nortriptylin), was in Analogie auch beim CFS gegeben wird. Beim CFS haben sich stufengerecht aufbauende physische Übungsprogramme bewahrt, um der Dekonditionierung entgegen zu wirken.

Tabelle 1

1. Neurasthenie/chronisches Erschöpfungssyndrom/Fibromyalgie: wichtigste Differentialdiagnosen:

Syndrom/Krankheit	Bemerkungen
Hypothyreose (Hyperthyreose), M. Addison	
Zöliakie (einheimische Sprue)	
Anämie	Kopfweh!
chronische Hepatitis	
AIDS (HIV-Encephalitis, PML)	Hirn-MRI, Liquor
Neurolues: progressive Paralyse	Persönlichkeitsstörung / Demenz. Liquor!
Neuroborreliose	„tertiäre" Form mit ZNS-Beteiligung
orthostatische Hypotonie / orthostatische Intoleranz (PoTS)	evtl. Sudor, Palpitationen im Stehen
multiple Sklerose (MS)	transiente neurologische Ausfälle
Myasthenia gravis pseudoparalytica	belastungsabhängige muskuläre Ermüdung
chronisch inflammatorisch-demyelisierende Polyneuritis (CIDP)	symmetrische Paresen + Sens-Störungen
periphere Hyperexzitabilitätssyndrome*)	Muskelkrämpfe, Myokymien, Insomnie
	evtl. paraneoplastisch
Stiff person syndrom	Anti-GAD-Antikörper, evtl. paraneoplastisch
Polymyositis	druckdolente Muskeln, Muskelenzyme
sLErythematodes, Arteriitis temporalis/cranialis	ANA, Rheumafaktoren
chronischer Aethylismus / Sedativa-Abusus	
Schlafapnoe-Syndrom (SAS)	Tagesschläfrigkeit
psychophysiologische Insomnie / Restless legs-Syndrom	Einschlafinsomnie
Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung (ADHD)	
para- und postinfektiöse Müdigkeit und Myalgien	
Reizdarm („colon irritabile", IBS)	
Anorexia nervosa	
Angststörungen	
somatoforme Störungen	
Depression / „Burn-Out"	

*) Muskelkrämpfe-Faszikulationen-Syndrom, Neuromyotonie, Chorée fibrillaire de Morvan
Labor: spannungsabhängige AK geg. Kalium-Jonenkanäle

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Myalgien und Krämpfe

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Die Muskulatur hat zusammen mit den ossären, artikulären und ligamentären Strukturen neben ihrer Hauptrolle in der Motorik auch eine Schutzfunktion inne. Schmerzfasern der Muskulatur sind einerseits die unbemarkten und langsam leitenden C-Fasern und vermitteln vorwiegend die Chemonozizeption. Darüber hinaus vermitteln die rascher leitenden bemarkten A-Delta-Fasern die Mechanonozizeption. Die Schmerzen stellen ein Warnsignal einer drohenden Gewebezerstörung dar.

Myalgien und Krampfe erleben die meisten Gesunden. Beim Muskelkater handelt es sich um die Folge einer individuell übermässigen muskulären Belastung, wobei exzentrische Muskelarbeit (z.B. Bergablaufen, Skifahren) gegenüber konzentrischer Muskelarbeit (Velofahren) einen besonderen Provokationsfaktor darstellt. Es handelt sich um einen Ruheschmerz mit Belastungskomponente, welcher Stunden nach einer Belastung auftritt, auch durch Muskelpalpation können die Schmerzen verstärkt werden. Die Beschwerden halten nicht langer als 1 Woche an.

Muskelschmerzen gehören zu den häufigsten Anlassen einer Arztkonsultation. Die potentiellen Ursachen sind sehr vielfältig. ln der Regel erlauben Umstände und Begleitsymptome des jeweiligen Krankheitsbildes die pathogenetische Zuordnung des Schmerzsyndroms, die klinische Untersuchung die topische Zuordnung. Schwieriger ist es, wenn die Myalgie das einzige Symptom bzw. das vorherrschende Leitsymptom ohne klinisches Korrelat darstellt.

Dem Patienten geht es darum, das lästige Symptom los zu werden. Der behandelnde Arzt hingegen muss denjenigen Patienten erkennen, dem er eine rationale Therapie anbieten kann oder bei dem eine Therapie sogar dringend indiziert ist.

Muskelkrämpfe

Von „krampfartig“ beschriebenen Myalgien gilt es eigentliche Muskelkrämpfe abzugrenzen. Dies sind schmerzhafte, unwillkürliche und palpable Kontraktionen des Skelettmuskels, die über Sekunden bis wenige Minuten anhalten. Sie können sowohl den gesamten Muskel als auch nur einen Teil betreffen, greifen aber nicht auf den Antagonisten über. Durch Willkürinnervation des Antagonisten oder passiver Dehnung des betroffenen Muskels können die Beschwerden gebessert werden. Bei den meisten Betroffenen sind die Krämpfe selten und harmlos. Prädisponierende Faktoren stellen muskuläre Überbelastung, höheres Lebensalter, Schwangerschaft, Störungen des Salz-/Wasserhaushalts, Dialyse, Genussgifte

wie Alkohol und Nikotin, Medikamente, Hepatopathie, internistische Polymorbidität, und orthopädische Probleme dar. Nur bei einem kleinen Teil der Patienten zeigen Krämpfe auf eine neuromuskuläre Erkrankung hin. Heftiges und häufiges Auftreten unklarer Ursache sollte aber Anlass zur Weiterabklärung geben.

Die Basis der Behandlung bilden physikalische Massnahmen und die Vermeidung prädisponierender Faktoren. Sollte dies nicht ausreichen, können in zweiter Linie Magnesium oder Medikamente mit membranstabilisierenden Eigenschaften eingesetzt werden. Die diesbezüglichen Studien sind durch ihren begrenzten Umfang und die hohe Placeboansprechrate gekennzeichnet. Bei nächtlichen Crampi wird Magnesium 3 x 5 mmol empfohlen. Chinin in der Dosis 200 - 500 mg hat hier die beste Wirkevidenz inne, jedoch sind potentielle Nebenwirkungen zu beachten.

Neben Kopfschmerzen, Tinnitus und Schwindel sind insbesondere Opticusatrophie und Herzrhythmusstörungen relevant, so dass im Einzelfall eine Nutzen-/Riskoabwägung und eine kritische Kontrolle des Therapieeffektes vorgenommen werden sollte. Alternativen bestehen in Gabapentin 600 - 1200 mg tgl. oder Mexiletin 300 mg. Bei familiärer Neigung zu Krämpfen ist möglicherweise der Calciumantagonist Verapamil in der Dosis 120mg nützlich. Bei Schwangerschaftskrämpfen ist Chinin kontraindiziert, es wird Magnesium 5 mmol morgens und 10 mmol abends empfohlen. Belastungsabhängige Krämpfe ohne hypotone Dehydratation können auf den Kalzium-Antagonisten Nifedipin bessern. Bei Hepatopathien mit Aszites wird die parenterale Gabe von Humanalbumin empfohlen, zur oralen Behandlung werden Vitamin E 400 IU oder Taurin vorgeschlagen. Hamodialyse-assoziierte Krämpfe können durch die Infusion hyperosmolarer Lösungen vermieden werden. Crampi im Rahmen einer peripheren arteriellen Verschlusskrankheit sollen auf Pentoxiphyllin ansprechen.

Zur Behandlung von Crampi haben sich nicht durchgesetzt: Phenytoin, Dantrolen, Amitryptilin und Calcium.

Muskelschmerzen ohne Myopathie

Muskelschmerzen sind schlecht lokalisierbar und häufig schwierig von Schmerzen aus den umliegenden Geweben (Gelenke, Bänder, Knochen) auseinander zu halten. Möglicher Ursprung der Schmerzen können auch Bindegewebe-, endokrine oder vaskuläre Erkrankungen sowie psychische Störungen darstellen. Flüchtige Myalgien in Rahmen von Virusinfektionen sind häufig.

Bei der Fibromyalgie handelt es sich um eine Erkrankung unbekannter Ätiologie mit Bevorzugung des weiblichen Geschlechts. Objektivierbare morphologische oder biochemische Veränderungen fehlen. Klinisch ist dieses Syndrom durch diffuse oder multilokuläre Muskelschmerzen, schmerzhafte Muskeldruckpunkte ohne pathologischen Palpationsbefund (tender points), Morgensteifigkeit, Adynamie, Insomnie und Depression gekennzeichnet. Die meist bilateralen Muskelschmerzen betreffen besonders Nacken-, Schulter-, Becken- und Gesässbe-

reich als auch Hüftregion und proximale Extremitätenabschnitte. Häufig werden Schlafstörungen wegen Myalgien und Steifigkeit beklagt. Manche Patienten nehmen eine Schonhaltung ein und können wegen des Bewegungsschmerzes Paresen vortäuschen. Die Diagnose wird gemäss den klinischen Kriterien des American College of Rheumatology gestellt.

Das myofasziale Schmerzsyndrom ist enger lokalisiert und meist akut einsetzend. Durch die sogenannten Triggerpunkte wird ein Übertragungsschmerz in einer für jeden Muskel spezifischen Referenzzone ausgelöst. Als auslösende Mechanismen werden hier Kontusionen, Distorsionen, anhaltender Druck auf die Muskulatur, muskuläre Überbeanspruchung oder Fehlbelastung sowie Zugluft diskutiert.

Myalgien gehören auch zu den im Vordergrunde stehenden Symptomen des Chronic fatigue Syndroms, wobei sich bei diesem ätiologisch unklarem Syndrom in der körperlichen und laborchemischen Untersuchung keine konstanten krankheitstypischen Befunde ergeben.

Da die Muskelbiopsie bei diesen Erkrankungen keine wegweisenden Befunde liefert, ist diese invasive Untersuchung nicht indiziert.

Die Polymyalgia rheumatica wird der Riesenzellarteritis zugeordnet. Es handelt sich um eine akut auftretende, zu einem chronischen oder remittierenden Verlauf neigende Erkrankung mit der Gefahr schwerwiegender Organkomplikationen im Rahmen der Vaskulitis. Die jährliche Inzidenz von 11/100.000 Einwohner steigt auf 843 bei den über 80-jahrigen, zwei Drittel sind Frauen. Die klinischen Leitsymptome sind bilaterale Steifigkeit und Schmerzen der Muskulatur und des periartikulären Gewebes. Oft setzen die Beschwerden akut innert einiger Tage ein und betreffen vorwiegend Schultergürtel und Nacken und/oder Beckengürtel. Die Beschwerden können auch Stamm- und Kiefermuskeln betreffen. Unter Bewegung intensivieren sich die Beschwerden, so dass viele Kranke diese vermeiden. Andere Erkrankte beklagen aber auch ein morgendlich betontes Beschwerdebild mit Muskelsteife (Morgensteifigkeit) und empfinden nach Bewegung Erleichterung. Zwei Drittel der Betroffenen beklagen Muskelschwäche, die sich jedoch nur in einem kleineren Prozentsatz objektivieren lässt. Begleitend können Allgemeinsymptome wie Malaise, subfebrile Temperaturen und Gewichtsverlust sein. Die BSR ist fast immer erhöht, durchschnittlich auf 65 +/- 26mm/h, jedoch werden auch zunehmend häufig Falle mit normaler BSR beschrieben. Die CK ist normal, Vaskulitisparameter negativ. Viele weisen eine Anämie und eine Erniedrigung der Serumalbumine auf. Elektromyographie und Muskelbiospie liefern hier kaum wegweisende Befunde. Die Biopsie der A. temporalis ist demgegenüber bei geringstem klinischen Verdacht auf Arteriitis indiziert. In der Therapie hat sich die Gabe von 30-60mg Prednison täglich bewährt. Hierunter werden die Erkrankten meist rasch beschwerdefrei. Eine niedrig dosierte Langzeitbehandlung über ca 2 Jahre sowie eine darüber hinaus gehende BSR Kontrolle ist empfohlen, um ein Wiederaufflackern der gefährlichen Vaskulitis zu erkennen.

Alkoholkonsum, Suchtmittelgebrauch und gesteigerter Arzneimittelgebrauch haben die toxischen Schädigungen des Muskels an Häufigkeit zunehmen lassen. Das klinische Bild kann variieren zwischen geringgradigen Muskelschmerzen bis hin zur Rhabdomyolyse. Eine Vielzahl von Medikamenten ist differentialdiagnostisch im Einzelfall zu erwägen. Eine aktuell häufiger werdende Fragestellung in neuromuskulären Sprechstunden ist die Frage nach Statin-assoziierter Myopathie. Grund hierfür ist die unklare Datenlage aus den evidenz-basierten kontrollierten Wirksamkeitsstudien der Statine. Aufgrund der sehr seltenen Nebenwirkung der Myotoxizität mit drohender Rhabdomyolyse werden Statine zunehmend für Muskelschmerzen verantwortlich gemacht. Wegen der unklaren Kausalität bei unspezifischen Symptomen wie Muskelschmerzen und leichter bis massiger CK-Erhöhung hat die American Heart Association 2004 empfohlen: Sollte sich bei einem Patienten mit oder ohne Muskelsymptome unter einer Statinbehandlung eine CK > 10-fache obere Normgrenze finden, ist die Statinbehandlung zu sistieren und Differentialdiagnosen zu erwägen, gegebenenfalls besteht wegen der Gefahr der drohenden Rhabdomyolyse die Indikation zur Muskelbiopsie. Bei unspezifischen Muskelsymptomen und unspezifischen CK-Erhöhungen (bis maximal 10-fache obere Norm) können Statine über einige wenige Wochen pausiert werden. Bei fehlender Besserung gilt es andere Ursachen zu suchen, das Statin darf weitergeführt werden. Wegen der unklaren Kausalität und der Problematik der unspezifischen CK-Erhöhung wird die Bestimmung einer Ausgangs-CK vor Beginn einer Statintherapie empfohlen.

Aus neurologischer Sicht können sich Erkrankungen des zentralen Nervensystems wie ein beginnendes Parkinson-Syndrom, fokale Dystonien, eine leichte Spastik oder auch ein Restless legs Syndrom mit dem Leitsymptom Myalgie präsentieren. Im Rahmen von Neuropathien kann es zu Myalgien und Krämpfen kommen. Insbesondere die schmerzhaften sensiblen und die motorisch (-betonten) Neuropathien können sich initial mit dem Leitsymptom Myalgie und/oder Krämpfen präsentieren.

Muskelschmerzen bei Myopathien

Der Muskelschmerz bei Myopathien wird in der Regel von einer begleitenden Schwäche, einer deutlich erhöhten Kreatinkinase sowie pathologischen Befunden in der Elektromyographie und Muskelbiopsie charakterisiert. Die Differentialdiagnose umfasst hier in erster Linie die inflammatorischen Myopathien autoimmuner Genese (Dermato- und Polymyositis, Vaskulitiden), ferner die infektiösen Myopathien, toxische Myopathien, die Formen der metabolischen Myopathien mit belastungsabhängigen Muskelsymptomen, zuletzt andere sehr seltene Myopathien mit im Vordergrunde stehenden Muskelschmerzen. Die Indikation zur dringlichen Abklärung und dann spezifischen Behandlung ist vor allem bei Verdacht auf inflammatorische oder toxische Myopathie gegeben, um eine Rhabdomyolyse mit ihren potentiellen Folgeschädigungen zu vermeiden.

Im Falle von Muskelschmerzen mit normalem Neurostatus ist die Wahrscheinlichkeit einer fassbaren Myopathie sehr klein. CK und EMG liefern meist nicht wegweisende Befunde. Der Goldstandard der Myopathieabklärung, die Muskelbiopsie, liefert beim Symptom Myalgie gemäss einer aktuellen Studie bei 240 Patienten lediglich in 2% der Falle spezifische Befunde und bestätigt damit die empirische Erfahrung des Myologen. Nur in der Subgruppe der belastungsabhängigen Myalgien und CK > 7-fach der oberen Normgrenze war die Wahrscheinlichkeit für eine metabolische Myopathie erhöht. Die Indikation zur invasiven Weiterabklärung mittels Muskelbiopsie sollte also nur bei streng selektionierten Patienten gestellt werden. Patienten sind wegen häufig unrealistischen Erwartungen an die Ursachenfindung mittels Muskelbiospie über diese Umstände aufzuklären.

Zusammenfassend stellen isolierte Muskelschmerzen aus neurologischer Sicht ein unspezifisches Symptom dar, welches aufgrund der weiten Differentialdiagnose oft zu breit angelegten, manchmal auch invasiven Abklärungen führt. Meist ist das Resultat für Patient und Arzt enttäuschend. Vor einer ungezielten, muskelbioptischen Abklärung lohnt es sich daher, anhand einfacher klinischer Kriterien und weniger paraklinischer Zusatzuntersuchungen die Differentialdiagnose der Myalgie einzuengen.

– Bei subjektiven Beschwerden wie Schmerzen sind wir auf die exakte Anamnese angewiesen. Handelt es sich um Schmerzen in Ruhe und/oder Belastung? Im Gegensatz zum Muskelkater treten bei Störungen des Muskelstoffwechsels Myalgien meist unter Belastung auf, nicht danach. Wie ist die Verteilung? (Myopathien sind meist proximal und symmetrisch) Lassen sich auslösende Faktoren eruieren? Was sind Faktoren, welche die Schmerzen positiv oder negativ beeinflussen? In welcher ggf. differentialdiagnostisch wegleitenden medizinischen Risikosituation befindet sich der Patient?
– Liegen zusätzliche muskuläre Symptome wie Schwäche oder Ermüdbarkeit vor?
– Bei Krämpfen gilt es primär die prädisponierenden Faktoren zu beachten und zu beeinflussen.

• Bestehen andere neurologische Symptome (sensible Störungen, Pyramidenbahnzeichen, Bewegungsstörungen)?
– Familienanamnese?
– Auftreten systemischer Symptome (Fieber, Arthralgien, Hautausschläge)?
– Resultate der Zusatzuntersuchungen: Erhöhte CK (Ausmass und Verlauf)? Labor mit Zeichen der systemischen Affektion (BSR, Blutbild)? Glukose, Leber- und Nierenfunktion, Elektrolyte und Schilddrüsenlabor? Pathologische Elektroneuromyographie?

Viele Patienten mit isolierten, auch intensiven Myalgien verbleiben ohne definitive Diagnose und werden letztlich häufig dem Fibromyalgiesyndrom zugeordnet. Eine für Arzt und Patient unbefriedigende Diagnose, spezifische Behandlungsmöglichkeiten liegen nicht var.

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Est-ce que c'est vous-même dans la glace? - the Phenomenology of Rorschach Expressive Constraint

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Abstract: From the Rorschach Construct Scales, a sixth factor has been separated – termed Emotional and Expressive Constriction – in addition to the five established (Big Five) components of personality. Taking into account recent warnings that statistical techniques have the power to take away from the individual's interaction with the clinician, it is concluded that this *Constriction* factor in Rorschach-based data sets is a measure of the phenomenology of the Rorschach process, representing not only the client's disposition, but also reflecting the clinician.

Key-words: Rorschach, Expressive Constraint, Factor Analysis.

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Introduction

Is the Rorschach a valid clinical tool? This question has been raised, and answered, over nearly a century of study. Recent meta-analytical studies have shown that on the question of reliability, the Rorschach stands comfortably alongside many other medical and psychological test procedures (1), and the intuitively apparent (or intuitively absent) validity of describing images in ink blots stands vindicated by this analysis of published evidence. Following in an *almost seamless logical progression*, there is a seductive symmetry which can be inferred from the statistical vindication of Rorschach: if numbers and statistics can shore up the foundations of our confidence in Rorschach, then the same tools (numbers and statistics) may likely add substance to the interpretative process when Rorschach is used in the clinic.Comforting and appealing as symmetry may be, that same quality of balance may be no more than a reflection in the mirror – nothing new, just a virtual representation of what we want to see. And applying this caution to the question of Rorschach clinical interpretation, we should be prepared to wonder whether statistics have added to and strengthened, or *peut-être* taken away from the service we aim to provide for each client.

Science, Measurement and the Phenomenology of the Clinical Interview

Whenever we are measuring facets of personality, and particularly when we are considering psychopathology, the rigorous application of the scientific method is of supreme importance, and the scientific method as a foundation of the psychological sciences is *very nearly undisputed.*

"Almost seamless logical progression"? – "Very nearly undisputed"? There has always been an undercurrent of distain towards the introduction of rigorous science in the clinic. Perusal of the literature may reveal that although this caution may be faint in quantity, it is stark in quality. Barthélémy (2) has presented in very readable form a powerful discussion of the methods of the *psychopathologue* (the science-based measurer of personality) and has contrasted their strictly quantitative approach with the *phenomenology* of the clinical situation. Although it is possible to interpret Barthélémy as defining a gulf rather than an overlap between the two approaches to understanding the human (psychological) condition, the present paper concludes that recent work by the scientific/statistical fraternity (the *psychopathologues*), employing the powerful tool of factor analysis with the Rorschach, has given empirical and statistically irrefutable evidence of the importance of phenomenology in personality assessment – and particularly in the case of the Rorschach.

In support of the notion of overlap between the two apparently disparate schools of thought, the present report submits that recently-produced groups of Rorschach descriptors (3) can be seen to demonstrate the proposition that part of the Rorschach personality profile actually relates to the clinician rather than the client. To

provide the practising clinician with an informed position from which to judge this suggestion, the present paper:

a. briefly reviews those aspects of factor analysis which are critical to the present issue,

b. reminds the reader of the extant literature discussing the individual clinical client/therapist interaction (the phenomenology of the consulting room situation),

c. concludes that the recently-established Rorschach measure of *Emotional and Expressive Constriction* is at least tainted by, or at worst entirely representative of, the therapist and does not provide a genuine and idiosyncratic facet of the client's personality.

Factor Analysis – a Review

Notwithstanding the virtual quagmire of prior works relating to the technical aspects of Factor Analysis (FA), it is none-the-less appropriate to briefly review the key aspects of this tool – at least those aspects which bear upon present paper's proposition.

It is the role of FA to take the responses to a bank of items administered to a number of subjects, and the analysis forms groups of these questions. These *groups* are seen to define the underlying *factors*. Although that process of extracting factors (which is for practical purposes the selection of coherent groups of items among a diverse set of questions) is simple enough in concept, there has been extensive discussion about the best way of using this powerful tool, particularly in the case of personality research. While there is a strong history of discussion about the validity or meaning different facets of personality and the role of FA in this field, the issues discussed may be theory-ridden and the individual client's personality is left out of the equation: see for example the works of Livesley et al (4) or of Molenaar, (5).

Regardless of theoretical issues, two "Global Truths" (GT) of FA remain clear:

> GT-I: That FA will inevitably return "groups" of items (descriptive phrases, questions, or any other variable which generates a quantitative response) based upon shared variance
>
> GT-II: That each factor (whether "weak" or "strong") will influence the conceptual direction (and hence the item composition) of all other factors in a manner analogous to a group of similar-poled magnets all trying to point "as far away from each other as possible" while in isolation each one would point North. Therefore adding or removing a particular grouping of items will necessarily alter the factor structure resulting from analysis of the whole item pool.

When Factors Beget Factors

As an established example of the appropriate use of FA in psychological measurement, consider the development of the Profile of Mood States (POMS) (6). Here, starting with a large pool of mood descriptors, FA was employed in a sequential process of eliminating the less robust items (less coherent) items. At length, after multiple passes over multiple groups of respondents, the authors arrived at six groups (six moods) which seemed useful and which appeared to refer to the same six robust underlying factors upon repeated analyses. Review of the items in each of the six groups easily led to the POMS titles such as *Depression, Anger, Fatigue* etc.

The development of the POMS serves to illustrate the way that FA can simplify a set of data (relating to mood, to personality, or to other measurable qualities). One commences with many items, too many items is the ideal situation, and then the application of FA ideally produces meaningful groups which makes the assessment and interpretation process more manageable.

But there are situations where FA may not sort things out. In the development of the POMS certain descriptors relating to *friendliness* and to *isgust* were first distinguished within, and subsequently deleted from, the item pool. But the opposite approach could have been used: McNair et al (6) could have added more descriptors to reflect these two abandoned mood qualities. And as more weak factors showed up, more and more items could have been added to strengthen and confirm the inevitably-appearing new facets of mood, and at the same time distorting those factors which had previously seemed robust (*see GT-II* above). This method (adding new items to weak factors) will almost always create even more new factors. This approach is not without its devotees: Shedler and Westen (7) have employed FA to define multiple personality facets – they gave many different descriptors to the analysis and they obtained many different factors.

To recapitulate:

- factor analysis can be used to simplify an item bank into several main constituents, and this "simplification" involves the removal of weaker items; or
- the same computational technique (FA) can be used to complicate the picture by first isolating robust factors and then sequentially adding items to the previously-feeble groupings.

Putting aside technical considerations such as oblique or orthogonal models of FA, one should bear in mind, and one should carefully choose between, these two distinct paths.

Complicated or simple, the construction of a quantitative measurement of personality can be seen to rely upon this same technique. This broad-brush description of test development is true even in the case of the original MMPI (see (8)) where the initial separation into ten "clinical scales" was done long before

computers could cope with a factor analysis of 566 items. Loosely speaking, one could regard the derivation of those "groups" as a style of part-intuitive and part-empirical factor analysis, representing as it did the process of (by whatever means) sorting out a large item pool into more or less coherent groups, considering if the measurement was "robust" (in that case the notion of robust being aligned with the idea of "clinically useful"), and eliminating from this or that group those items deemed "non-coherent" with the construct under consideration.

With the advanced capacity of modern computers to handle large data sets, the development of a personality (or any other quality) profile follows this path: pose multiple questions to a large group of respondents, and remove the weakest items (for example, by using FA). Repeat the process to cross-validate the putative factors. Finally the residual item groups represent the most robust item groups (*factors*) which will be seen as measurable (and likely even *tangible*) facets of personality. Over more recent years the Big Five was born, and confirmed, in this manner. The same five strong factors are regularly found (see reference (3)). It is, of course, beyond dispute that if one were to add more questions which relate to qualities distinct from those covered by the Big Five, then one would be sure to define a new factor. That would be no surprise – and this simple, self-evident truth should be borne in mind when "new factors" are discovered.

From the above review, we can see that Factor Analysis produces factors, and these may (or may not) be appropriately regarded as characteristics of a client. Whether or not these factors or "groups of items" may appear as credible or recognisable personality constructs, they are in the first instance numerical groups. They are defined by the shared variance in the underlying group data. Individual clinical clients do not necessarily represent an instance of "shared variance", and it has been recognised that the application of numerical methods may serve to *taint* [1], rather than to *identify* or clarify, the very quality (*le caractère*) which we seek to measure (2). This tainting is, in the first instance, predicted by *Global Truth II* (above), but the distorting intrusion can reach further than the logical limitations of that warning: more than merely *distorting* the measured aspect of an individual's personality, it is possible to use FA to *add qualities* which do not even exist in our client.

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[1] la soumission de l'évaluation scientifique d'une recherche à l'existence de données chiffrées ou pour le moins quantifiées, le caractère suspect dont est entachée, en manière de conséquence et de réversibilité gratuites, toute démarche d'analyse qualitative, la réduction de toute forme d'implication subjective à l'arbitraire, l'affirmation abusive et donc erronée que le chiffre ou la courbe ne sont pas qu'une voie parmi d'autres pour effectuer des travaux scientifiquement recevables et productifs, mais l'unique moyen d'y parvenir et de les légitimer dans ce cadre, le danger enfin, par un entêtement systématique, à utiliser indifféremment les mêmes pratiques quelles que soient les circonstances ou les contextes d'études, quitte à ne plus avoir affaire qu'à des abstractions vides d'implications et d'applications concrètes, donc privées de sens. (3, p 251)

A Rorschach Factor – Expressive Constriction

In contrast to the method of *simplification* via FA leading to less items Mihura et al (3) used the approach of adding more items. In the various stages of their extensive data re-analysis, Mihura et al separately analysed items based upon the DSM-IV, also items relating to the Big Five (BF), as well as a set of Rorschach-relevant personality descriptors (the RCS). At length they had in hand a total of 14 personality factors: six from Rorschach, five from BF, and three from DSM-IV. The three DSM-defined factors, unsurprisingly, closely overlapped three of the BF scales (with correlations of 0.82, 0.70 and 0.62).

These multiple factors serve to re-affirm the proposition (*GT-I* above), that if FA is applied to a diverse set of responses, then factors will inevitably assert themselves. Furthermore the overlap of BF and DSM factors served to confirm that if items are talking about a similar notion, then factor analysis will likely bring them together (part of the proposition *GT-II*).

When the Rorschach-derived descriptors were submitted to FA, six factors had emerged, and from inspection of their content these six measures were not obviously parallel to the conventional robust facets of personality (DSM and BF). Four of the six Rorschach factors (really scales based upon the factors) had very poor correlations with the BF and the DSM scales. At this point the Rorschach-based groups could tentatively be regarded as describing potentially "new" personality dimensions. The next step taken by Mihura et al (3) was to enlarge the data pool by placing the Rorschach-derived items together with the DSM and BF items. The new conjoint factor analysis of items chosen from all fourteen factors would be expected to obey the two principles above (*GT-I* and *II*): factors would be indeed found; the composition (and conceptual direction) of each of these factors would be potentially influenced by the other factors within the entire item pool. Some items would likely be drawn into already robust vectors thus potentially modifying their flavour, while others would be pushed away from the existing throng of strong factors, defining one or more new groupings. In the end, the Big Five personality constructs were re-found, and most of the Rorschach items were subsumed by these omnipotent groups. However one almost-new Rorschach-only factor emerged – and from inspection of item content it was named *Emotional and Expressive Constriction* (EEC).

Let us consider this sixth "almost-new" factor, EEC, de nouveau. With regard to novelty, EEC is not entirely without precedent. For example *Restricted Expression* was one of 15 separable qualities described by Livesley et al (4) (acknowledged by Mihura et al (3)), and a conceptually parallel quality can be detected in the MMPI-2 secondary measure *Negative Treatment Indicators* which comprises items such as *when I have a problem it helps to talk it over with someone (**False**)* (8).

Consideration of the interactive implications of the above-mentioned MMPI-2 scale alerts us to the possibility that this new factor (EEC) is an indication, not of

an independent aspect of the client, but of the phenomenology of the Rorschach client-Examiner reciprocity. This proposition is not self-evident, since Mihura's data (3) was not from actual Rorschach encounters, but rather the data involved answers provided by an Observer describing somebody they knew quite well.

To establish the "phenomenological" underpinning of EEC, it behoves us to first consider the actual descriptors which define the factor, and then we need to look to the Rorschach measures which lie at the heart of these statements. The five *EEC* items were deliberately chosen to reflect the Rorschach/Exner measures of R (number of responses), Lambda, and of colour-related responses.

- *Trouble describing feelings thoughts and reactions* (R & Lambda)
- *Tightly controls the way he experiences feelings* (color)
- *Guarded and withholds personal feelings thoughts and reactions* (R & Lambda)
- *Tries not to express problematic feelings and ideas* (R & Lambda)

(3, p 30).

In the Rorschach consultation, these underlying measures (R and Lambda) have been shown *on average* (across a large group of clients and examiners) to depend upon the Examiner. There is a well-quoted and extensive literature on the influence of situational variables upon the client`s utterances, but for the present paper let us limit ourselves to the words of Exner (9). With adult clients: *in their 1978 study Exner et al demonstrated that adult patients, tested by their own therapists, gave an average of 10 more responses than patients tested by a stranger . . . elevations in color responses . . . largest differences involve values for* ***Lambda*** (9, pp 16 and 18). And a similar Examiner-effect is reported for children: *tested by own teacher* R = 38.2, but a dramatically restricted output when t*ested by unknown teacher* R = 22.6 (ibid, p 17). Based upon almost a century of writings which agree with this point (eg 10, 11 and 12), we can confidently conclude that for a more familiar examiner, *on average* there will be a greater score for ***R***, more colour responses and elevated ***Lambda*** compared to an examination conducted by a stranger. The dependence of ***R*** (and the other measures) upon examiner-familiarity *in general*, even when using identical instructions, is an uncontroversial proposition *in general* – and like all generalities, it is precisely based upon the phenomenology of multiple individual cases.

If the Examiner-effect is an uncontroversial fact "on average", then logically it is equally uncontroversial that in each case of an individual client, the critical measures which underlie Mihura's *Emotional and Expressive Constraint* will depend upon the rapport between the client and the clinician – in effect, the phenomenology. And given the indelible truth of this proposition as applied to the Rorschach consultation, the logical circle of cause-and-effect closes to include the corresponding qualities recorded by the "observers" in Mihura's experiment:

low scores were given on items which were statistically interpreted as defining "Expressive Constraint" when the Observers were describing a person with whom they had impoverished rapport. A phenomenological interaction at best – a reflection of the Observer at worst. The fact that this EEC factor was statistically spurned by the well-established Big Five personality qualities serves to support the idea that EEC is not merely quantitatively different (in the factorial sense) but is also qualitatively different from established personality measures – it depends upon the phenomenology of the Observer (or Examiner) relationship with the subject being measured.

As an example of the potentially misleading nature of this sixth factor, I had a client (a boy aged ten years) who had the habit of taking things. He stole the lunch from other students, and at his own home his parents had placed a lock on the refrigerator. Social Workers and other helping professionals had been called in, without effect. It goes without saying that this lad had a poor rapport with the significant adults in his life (at home and at school). Not surprisingly it was next to impossible to create a positive therapeutic relationship with him – at least not straight away. Before turning the first card, one could all but guarantee the finding of Mihura et al's "Expressive Constriction", where this would be shown by a low R score. The lad gave almost no responses to the plates, regardless of how the interrogative questions were phrased. At length I showed him the same plates with the same formal Rorschach prompts (*what could this be* etc, taken from Exner (10)) on a computer. He immediately became a fountain of responses. He seemed to regard me in this new setting as his colleague and aide, asking me how to spell this or that word, and boasting to me over his shoulder how he was now going to tell the computer that this looked like an elephant (or whatever). The computer had taken on the role of the Examiner; I was a mere bystander. It was evident that this new Examiner had an excellent rapport with the client, and as an inevitable consequence of this good rapport, the lad no longer suffered from "Expressive Constriction": his R score had become normal. Other details of this case are irrelevant here. The important point is that we had a lad who appeared to suffer from Expressive Constriction, but in whom the problem disappeared when examined by his friend the computer. What we really had was a boy who started off a relationship with serious negative transference towards (probably any and all) adults.

Conclusion

Just as the professional approach to the understanding of personality can be separated into two qualitative domains, typically labelled *phenomenological* and the *statistical psychopathologue* domain, so too the components which combine to make up a person can be separated into the same two groups. As the standard personality assessment tools such as the Big Five have steadily homed in upon the appropriate targets of statistical tools (the stand-alone

qualities which are measurable), and steadily the process of evolutionary refinement has rendered these long-standing tools more and more selective in their targets and hence more and more useful in their pronouncements. Clinical-focussed specialists have kept an eye upon the clinical interaction as the key to their work – that is the phenomenology of the consultation. Not surprisingly, when the phenomenologists have offered descriptions of their clients, then they have preferred descriptive qualities that are tilted towards the clinical interaction. Following logically from these two equally valid strands of psychological activity, it is credibly predictable that when the descriptive terms of the phenomenologists are surrendered to the analytical processes of the psychopathologue, then the outcome may be confusing – and the cloud of uncertainty hovering above the outcome will make it difficult to decide whether the measurement tools born from this union are measuring indelible and idiosyncratic client qualities (usually termed personality factors) or whether at least some of the qualities which have been isolated are more a result of the interaction twixt client and therapist – to a greater or lesser extent, a reflection of the clinician.

For the future, it would make sense to encourage our young clinicians (it may be too late for those already established) to recognise firstly that their own clinical presentation and attitude will have an effect upon what happens next. Twenty years ago (in an almost entirely overlooked analysis which has never yet been cited in the relevant literature), Beeby, Broussine and Guerrier (13) described seven different "role responses", or interactive styles, which a clinician might adopt in dealing with a client[2]. Awareness of these distinct role profiles would help clinicians to manage the phenomenology to the client's best advantage, rather than blindly accepting the institutionalized structure which, it has been recently suggested, is imposed upon clinicians through their training (14). For the open-minded clinician, the most useful descriptions of a client will include the immutable (or at least stable) qualities which make up the *psychopathologues'* measures of personality, together with the interactive qualities which are situation-specific. It would make even greater sense for entrants to the field of psychological assessment to be encouraged to recognise the manifestly phenomenological components which exist in clinically-derived measurements. Quite daunting appears the task of sorting out the phenomenology from the statistics in the interpretations by Rorschach

[2] Beeby et al's (13) seven roles responses for the helping professional: **Voyeur:** keen to "interact" with people, to collect information about them, but aims to change as little as possible; **Missionary:** strongly believes in one particular approach or view of life, and always try to direct the client to adopt these ideas; **Skilled Craftperson:** recognised as being technically skilful - clients present new opportunities to try out new interventions and new techniques; **Therapist:** all people. are capable of growth, of learning more, of improvement in the way they do things; **Catalyst:** an important part in helping is to question the current way of operating and to manage the process of change and modernization. **Conscientious objector:** has serious problems about being associated with certain groups who do things in a way he/she does not approve of. **Entrepreneur:** It hardly matters about the needs of the client, as long as they will pay for the service.

practitioners, however as a starting point the MMPI-2 Negative Treatment Indicators (TRT) (9) provides a relatively uncontroversial example of a client "measurement" which (despite being based upon self report data) in fact speaks of the respondent's experience of the clinical interaction rather than describing the client in isolation. On the TRT scale, we are told that *high scorers . . . have problems they are not comfortable discussing with anyone* (9, p 44, emphasis added). "Not comfortable with anyone"? Not until they experience the right phenomenology, anyhow.

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Vignette historique

Docteur Charles MARX

1903-1946

Georges Erasme MULLER

J'habiterai mon nom
Saint-John Perse (1887-1975)

Abstract:

Charles Marx (1903-1946) an outstanding Luxembourg physician was a communist. He had very well succeeded in his medical studies in Paris starting as an interne (1929), to become «chef de clinique chirurgicale», then a «Lauréat de l'Académie de Médecine» and finally a member of the «Comité de l'Association française de Chirurgie» (1935). He founded his own hospital (50 beds) in Ettelbruck. There, in 1940, he helped two interned French airmen, to escape to France. Charles Marx escaped himself, with his family, just before the German invasion. He briefly directed four French hospitals, in Nevers and in Quillan. In July he founded the first resistance group of the «Armée secrète», which in May 1943 was followed by a first maquis in the western Pyrenees. In June 43, he was condemned to death «in absentia» in Montpellier by the Nazis. In February 1944 Charles Marx was appointed medical commander of the FFI and chief health manager of the Resistance in the oriental Pyrenees. In September 1944 he took part in the liberation of Lyon. In October, being the delegate of the medical resistance council, he was named attaché to the Health Minister and was charged to organize French-American military surgical structures.

End of July he took up the management of the Ettelbruck hospital. In November 1945 he was nominated minister of Public Health in Luxembourg. In June 1946 Charles Marx and his Rumanian wife lost their lives in a car accident.

Key words: Charles Marx, Luxembourg, Communist, Medical career, World War II France, Resistance, Public Health minister, Biography.

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Nomen est omen. Qui suis-je? Tout enfant et adolescent à la recherche de son identité se pose cette question. S'il découvre qu'un personnage illustre portait le même nom que lui, il en sera tout fier et essayera d'imiter son homonyme qui a réussi dans la vie.

Fig.1. La famille Marx-Siegen en 1916. Charles, treize ans, fréquentait l'Athénée de Luxembourg, comme Robert Schuman, 19 ans plus tôt. (Photo Archives Nationales du Luxembourg.)

Louis Charles Marx est né le 26 juillet 1903, 5 rue Arsenal, au centre de la ville de Luxembourg, à deux portes de la librairie Robert Hausemer. Son père Louis Marx débuta comme apprenti boulanger, devint représentant de commerce et finit comme agent d'affaires. Il épousa Emilie Siegen, la fille du vétérinaire de l'Etat, Charles Siegen (1842-1904), qui n'habitait pas loin dans la rue Philippe II.

Charles Siegen, avait organisé, pendant la guerre franco prussienne de 1870/71, les convois de secours des médecins luxembourgeois sur les champs de bataille à Sarrebruck et à Metz. Emilie donna naissance, d'abord à Louis Charles, puis à trois filles dont l'aînée ne vécut qu'un jour. Louis Marx, le père, semble avoir été un débrouillard qui avait le sens des affaires.

Louis Charles, le fils, était un lycéen brillant, aux contacts faciles, qui gardait comme amis, d'autres lycéens remarquables comme Raymond Kahn (1904), émigré à New York au début de la guerre, comme René et Tony Neumann, riches industriels, Jean Harpes (1901) pédiatre, Henri Loutsch (1905-1979) chirurgien et fils de médecin, Gust Trémont, notre sculpteur national, ainsi que Nic Schumacher (1901-1962) omnipraticien et Charles Jones (1898-1963) obstétricien, ses futurs complices pendant la guerre, pour n'en nommer que quelques-uns.

Tout ceci n'explique pas encore pourquoi, Charles Marx, en 1919, à l'âge de 16 ans, fonda les «Jeunesses socialistes» et pourquoi, en 1921, à l'âge de 18 ans, il fut à l'origine de la rupture de ce mouvement avec le parti socialiste quand ses adeptes se transformèrent en «Jeunesses communistes». Très jeune il semblait déjà disposer d'une autorité naturelle considérable.

L'origine du choix marxiste s'explique probablement, d'une part dans l'intelligence «cartésienne» de Charles Marx qui découvrit dans la logique du matérialisme dialectique une analyse sociologique scientifique de l'histoire, offrant une méthode de pensée et d'action, qui justifiait l'espoir d'en modifier le cours vers une société plus juste, en attribuant la plus-value des matières brutes en marchandises, au travail de l'homme plutôt qu'aux spéculations capitalistes ou aux privilèges des classes.

D'autre part notre jeune étudiant, peut-être sous l'influence de ses parents et de ses grands-parents, semblait décidé d'aider les hommes, tous les hommes, sans discrimination aucune, décision renforcée par la tradition hippocratique transmise aux médecins, depuis plus de deux mille trois cents ans.

Les études médicales de Charles Marx furent les plus brillantes qu'aucun étudiant luxembourgeois n'eût réussies jusque-là. De 1925 à 1927 il démarra doucement, assistant en tant qu'élève libre aux cours de la faculté de médecine de Strasbourg, discutant passionnément dans les bistrots des étudiants, tout en maîtrisant le rythme annuel des candidatures et des doctorats, pour le diplôme d'Etat au Luxembourg, qu'il passa en septembre avec distinction. Ce système archaïque grand-ducal gâchait aux étudiants, tous les ans, les vacances d'été, déjà moroses après deux semestres universitaires peu satisfaisants pour des élèves «libres», pas vraiment impliqués dans la vie hospitalière, et sans équivalence des examens d'un pays à l'autre.

Marx s'inscrit parallèlement pour le diplôme universitaire français et, en 1927, déménage à Paris. En décembre son père meurt et Charles doit assumer ses responsabilités de chef de famille pour sa mère et ses sœurs cadettes. Il n'y a plus de temps à perdre. En 1929, dans un délai record, il devient le premier Luxembourgeois à réussir le concours de l'Internat des hôpitaux de Paris, exemple suivi en 1930 par Henri Loutsch et en 1932 par Simon Hertz (1907-1983). Dès 1929 Marx travaille comme interne à l'Hôtel Dieu, puis à l'hospice de Paris Bicêtre. En août 1930 il épouse, dans le 14^{e} arrondissement, Lucienne Aubouéron, une modiste de Nevers, et réussit en même temps, ses trois doctorats indispensables pour le diplôme d'Etat au Luxembourg, avec distinction. A Paris il est promu Chef de clinique chirurgicale à la Faculté de médecine, fonction qu'il assume d'octobre 1935 à février 1936. En 1935 il publie sa thèse de doctorat, toujours avec distinction, sur «Le fonctionnement de l'estomac après gastrectomie» une approche originale aux résultats postopératoires, par l'analyse physiologique et l'évaluation clinique globale de l'évolution du malade.

Marx est élu membre titulaire de «l'Association française de Chirurgie», ses travaux lui valent le titre de «Lauréat de l'Académie de médecine» et il devient membre du comité de l'Association française de chirurgie.

En 1936, n'ayant trouvé aucune salle d'opération accessible dans les hôpitaux de la ville de Luxembourg, il retourne à Ettelbruck où il fonde la clinique privée Saint Louis, disposant de cinquante lits. Au rez-de-chaussée, tous les deux nommés par la Croix rouge, le docteur Nicolas Huberty (1890-1976) dirige la pédiatrie-néonatologie et le docteur Prosper Schumacher (1878-1941) le dispensaire de tuberculose.

Fig.2. L'équipe hospitalière du Dr. Charles Marx à la clinique St. Louis à Ettelbruck avec les dix sœurs alsaciennes de Niederbronn, une image qui reflète bien l'autorité calme d'un chef dirigeant une équipe bien soudée. (collection Arthur Muller)

Ne disposant pas du personnel qualifié indispensable, Marx réussit à engager une dizaine de sœurs alsaciennes de la Congrégation du Très Saint Sauveur de Niederbronn, qui disposent d'une formation hospitalière sérieuse et seconderont avec dévouement et compétence ce jeune médecin très populaire, pourtant athée et communiste. Après la mort accidentelle du docteur Charles Marx en 1946, les sœurs alsaciennes demeurent fidèles à la clinique d'Ettelbrück et la dernière soeur ne rentrera à Niederbronn qu'en 1971.

Un exemple des décisions rapides du jeune chirurgien. Le 25 avril 1938 à Luxembourg, il divorce de Lucienne Aubouéron et, trois semaines plus tard, le 16 mai, il épouse, à Londres (Marylebone), Fernande Lucette Vasilescu de Ploesti en Roumanie. Trois mois plus tard, à Luxembourg, sa deuxième femme accoucha d'une petite fille.

L'exemple suivant de rapidité et de présence d'esprit, se joue dans un tout autre domaine. Le 2 avril 1940, pendant la drôle de guerre, un avion de reconnaissance français est obligé d'atterrir près de Niederfeulen. Trois occupants indemnes sont transférés à Luxembourg, pendant que les deux autres, le capitaine Marcel Pierre Faure et son adjudant-chef Charles Lherbiet, blessés légèrement, sont amenés à la clinique Saint Louis à Ettelbruck. Le docteur Marx enveloppe les Français de pansements, qui les font ressembler à des momies, et leur demande en plus de gémir à en fendre le cœur. Cette mise en scène empêche leur arrestation par deux gendarmes luxembourgeois qui, armés par Marx de certificats dramatiques, se postent devant la porte de l'hôpital. Les «grands blessés» libérés de leurs bandages et ayant cessé de gémir, sautent de l'autre côté par la fenêtre, où les attend la Packard puissante du docteur Huberty qui démarre en trombe, suivant la voiture du docteur Nic Schumacher de Dudelange avec son épouse, qui connaissent tous les passages non gardées de la frontière française, qui détecteront d'éventuels barrages et pourront guider leur contournement. Les gendarmes engagent la poursuite avec un certain retard, l'un dans une vieille camionnette et l'autre, le brigadier Huss, un surexcité qui, quand Fernande lui sourit au nez, réquisitionne le docteur Marx, sa femme et sa voiture, en brandissant un pistolet. Marx n'arrive d'abord pas à démarrer puis, Huss furax et Fernande amusée, n'avance que prudemment, respectant scrupuleusement toutes les limites de vitesse. Inutile de dire que les officiers français, disposant d'une avance confortable, passent en France, par le pont «Kieselbrücke» à Altwies. Généreusement Marx s'offre à rembourser à Huss l'amende qui lui sera infligée – comme une espèce de prime négative – parce qu'il n'a pas réussi à rattraper les fuyards. Notons que le «capitaine» Faure, plus tard promu général, offrira son aide précieuse aux Marx, évadés en France un mois plus tard.

Pendant que les couples Marx, Schumacher et Huberty s'apprêtent à fêter l'évènement dans le café Raus à Aspelt, leurs voitures sont repérées par une patrouille de gendarmes qui, de mauvais poil, notent les noms de tous les complices de cette évasion. Le procès verbal, vaut au «délinquant» Marx une convocation au tribunal de Diekirch le 8 mai 1940 suivie le 14 mars 1941, sous l'occupation allemande, d'une condamnation «per contumaciam» à huit mois de prison et une amende de 2000 DM. A cette époque les conceptions du bien et du mal, du juste ou du faux, évoluaient rapidement mais, imperturbablement, notre Justice continuait à faire son devoir. Le 10 mai les Allemands envahirent le Luxembourg, mais déjà le 9 mai, les Marx, avertis à temps, s'étaient réfugiés en France.

Par Paris et Nevers, – où Charles Marx assume brièvement la responsabilité médicale et chirurgicale de deux établissements hospitaliers en mai et en juin – à Montpellier, où en juillet il est nommé responsable du bureau de la Croix Rouge luxembourgeoise, il aboutit finalement à Perpignan.

Fig. 3. Quillan, chef-lieu cantonal, de quelques milliers d'habitants, à une vingtaine de kilomètres de la frontière espagnole, situé sur l'Aude, un torrent pyrénéen, né dans le massif du Carlitte en Espagne et descendant vers Carcassonne et Narbonne. Le modeste hôpital de vingt deux lits du Dr. Marx devient un relais important pour des milliers d'évadés épuisés et souvent malades, parmi eux de nombreux Luxembourgeois, avant leur passage en Espagne et au Portugal pour rejoindre, malgré l'opposition du gouvernement luxembourgeois à Londres, les forces alliées en Grande Bretagne. (Vieux Quillan – photo Patrimoine Quillan)

En décembre 1940 le couple reprend une clinique minuscule, appartenant au docteur Fabregat de Perpignan, située à Quillan dans l'Aude.

Le 18 mars 1941, à Quillan aussi, ils perdent leur petite fille Elisabeth, qui n'a pas encore trois ans.

En décembre 1941, Charles assume la direction d'un modeste hôpital, toujours à Quillan, au pied des Pyrénées, en louant et en transformant un hôtel de 22 lits. Dès mai 1942 le règne de terreur de Pierre Laval, imposé par les Allemands, s'étend à la «zone libre», qui sera envahie par les troupes de la Wehrmacht en novembre 1942. Les actions courageuses du docteur Charles Marx sont tellement nombreuses, qu'on ne peut les énumérer qu'en style télégraphique. Vous trouverez les détails dans l'excellent livre, bien documenté, de Giulio-Enrico Pisani.

Fig. 4. Charles Marx vers 1940. Collection Giulio Enrico Pisani.

* En juin 1942, il prend contact avec le réseau gaulliste Mithridate et organise deux filières (Elizabeth et Charlotte) entre Luxembourg et Londres, avec l'aide des résistants Albert Ungeheuer, Nicolas Gengler, Charles Reiffers et Eugène Léger.
* En juillet 1942 Charles Marx forme à Quillan avec Raoul de Volontat le premier groupe de résistance de l'Armée Secrète.
* En mai 1943 il crée un maquis dans la Haute Vallée de l'Aude.
* Le 5 juin 1943 Marx transmet le rapport et le croquis fourni par le docteur Schwachtgen de Mersch, sur les installations de Peenemünde, à

Londres. Du 16 au 18 août les lance-fusées de Peenemünde seront bombardées à deux reprises par la Royal Air Force. Le même mois, à la demande de la Gestapo, Charles Marx est condamné à mort «in absentia» par un tribunal de Montpellier.

* Le premier février 1944 il participe à la création des Forces Françaises de l'Intérieur (FFI) dont il est nommé Médecin Commandant et chef de l'administration sanitaire de la Résistance en région Aude et Pyrénées Orientales, zone France-Sud.
* Le 2 et le 3 septembre 1944, en tant que médecin commandant des FFI il participe à la bataille de libération de Lyon.

En octobre 1944 à Paris, en tant que délégué du Conseil médical de la Résistance, il est nommé Attaché au cabinet du ministre de la Santé, Pasteur Valléry-Radot.

Fig. 5. Dr. Charles Marx, (médecin, organisateur des FFI, maquisard, combattant …), Collection Giulio-Enrico Pisani.

En novembre1944 Charles Marx se réengage dans l'Armée française pour organiser des structures militaro-chirurgicales franco-américaines.

Le 30 juin 1945 il fonde avec Nic Kremer la Ligue des Réfugiés et Evadés Politiques Luxembourgeois (LPF).

Le 31 juillet 1945, Charles Marx reprend la direction de sa clinique à Ettelbruck.

Entre le début de sa carrière politique au Luxembourg, en octobre 1945 – conseiller municipal, député, ministre de l'Assistance sociale et de la Santé publique – et sa mort dans un accident de voiture le 13 juin 1946, il n'y a que huit mois, mais il a réussi:

– à régler les conditions de stage pratique des médecins spécialistes et des médecins omnipraticiens;
– à fonder le Conseil National pour la protection de la Mère et de l'Enfant

A elles seules, ces initiatives, deux premiers pas vers de vastes projets de l'organisation médicale, de la sécurité et de la justice sociales, nous font deviner quels progrès ce grand organisateur aurait réalisé, améliorant la médecine et la qualité de vie dans notre pays.

Le 13 juin 1946, nous avons perdu un grand médecin, un grand résistant, un homme généreux aux vastes visions pour l'avenir. Parmi nos médecins de haute qualité et nos résistants courageux – nous en avons eu quelques-uns dans ce pays – on peut certainement placer le docteur Charles Marx … sans oublier Fernande Vasilescu, son épouse roumaine, originaire de Ploesti, qui l'a aidé dans toutes les situations difficiles et qui est morte avec lui.

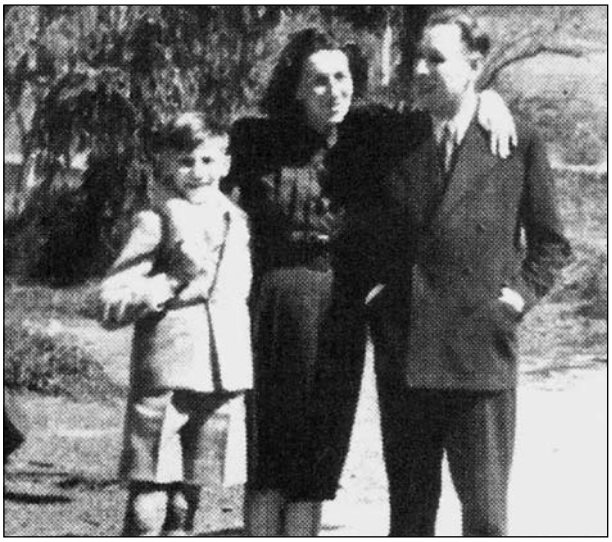

Fig. 6. Fernande Vasilescu et Charles Marx ayant perdu leur petite fille Elisabeth à Quillan le 18 mars 1941, n'ont plus eu d'enfant. Malgré tous les tourments, tous les dangers qui les entouraient, toutes les actions entreprises pour sauver des vies, ils ont trouvé le temps d'adopter plusieurs enfants, dont nous avons perdu la trace. Guy, bien soigné et heureux sur cette photo, en était un. (Photos Archives KPL)

Le 27 juin 1946, quatorze jours après sa mort, la «Clinique St. Louis» qu'il avait fondée à Ettelbruck en 1936, fut rebaptisée «Clinique Dr. Charles Marx».

Il est triste, comme toujours, de ne presque plus trouver son nom dans notre histoire officielle où l'on tend à oublier les communistes vaillants, un peu plus vite que les autres. Tout de suite après la guerre, nos résistants marxistes étaient fort respectés jusqu'en 1946 quand le «rideau de fer» – l'expression est de Winston Churchill – forma la frontière entre les Etats socialistes de l'Europe de l'Est, sous influence soviétique, et les Etats démocratiques et capitalistes de l'Europe de l'Ouest, sous l'influence des Etats-Unis.

Fig. 7. Charles Marx fut surtout décoré en France, «à titre posthume», et à Quillan, un espace porte son nom. Au Luxembourg, en 1945/1946 il fit une carrière politique éclair quand, après avoir sauvé bien des gens il entreprit de guérir son pays. Comme traces il en reste un boulevard dans la capitale, une tombe au cimetière Notre Dame et l'histoire de sa vie à raconter à nos jeunes.

En France, de Gaulle décora Charles Marx «à titre posthume» de la toute première «Croix de la résistance». Le général Koenig lui accorda, au même titre, la «Croix de guerre avec étoile de vermeil» et il fut nommé «Commandant de la Légion d'Honneur».

Le 17 avril 1947 les corps de la petite Elisabeth et de ses parents Fernande et Charles ont été rapatriés et re-inhumés au Cimetière Notre Dame à Luxembourg.

A Ettelbruck, l'hôpital que Charles Marx, le communiste, avait baptisé lui-même Clinique St. Louis et qui, après sa mort, le 13 juin 1946, avait été rebaptisé Clinique Dr. Charles Marx, fut rebaptisé Clinique St. Louis en 1963, quand le conseil communal conservateur trouva quelque tare morale dans son divorce et préféra rappeler St.Louis – fils de Blanche de Castille, roi de France, mort de la peste à Tunis pendant une croisade en 1270 et canonisé en 1297 – comme patron de l'hôpital d'Ettelbruck, situé pas loin d'un square modeste dédié à Charles Marx.

Parfois une histoire luxembourgeoise en vaut une histoire belge.

Un dernier souvenir d'un confrère qui se trouva au parloir des sœurs alsaciennes de la Congrégation du Très Saint Sauveur et y découvrit une grande photo du docteur Charles Marx, flanquée de reproductions plus modestes du Pape et de l'Evêque. Quand notre confrère s'étonna des proportions, la Mère Supérieure lui répondit fièrement:

«**Hien** war eisen Här»
(**C'était lui** notre patron)

Je remercie Giulio-Enrico Pisani, l'auteur de l'excellent livre «Charles Marx, un héros luxembourgeois», édition Zeitung vum Lëtzebuerger Vollek, 2007, où j'ai puisé presque toutes les informations qui ont servi à écrire cet article, complété par des détails fournis par mes confrères André Thibeau et Georges Theves. Monsieur Pisani et les Archives KPL m'ont autorisé à utiliser quelques photos de son beau livre.

Les publications des médecins, médecins dentistes, médecins vétérinaires, pharmaciens et biologistes chimistes luxembourgeois dans les revues scientifiques à l'étranger

High genetic diversity of Measles Virus, World Health Organization European Region, 2005-2006

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During 2005-2006 nine measles virus (MV) genotypes were identified throughout the WHO European region. All major epidemics were associated with genotypes D4, D6 and B3. Other genotypes (B2, D5, D8, D9, G2, and H1) were only found in limited numbers of cases after importation from other continents. The genetic diversity of endemic D6 strains was low and genotypes C2 and D7, circulating in Europe until recent years, were no longer identified. The transmission chains of

several indigenous MV strains may thus have been interrupted by enhanced vaccination. On the other hand multiple importations from Africa and Asia and virus introduction into highly mobile and unvaccinated communities caused a massive spread of D4 and B3 strains throughout much of the region. Thus, despite the reduction of endemic MV circulation, importation of MV from other continents caused prolonged circulation and large outbreaks, after their introduction into unvaccinated and highly mobile communities.

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Measles – Rubeola

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Measles is an acute systemic disease associated with a maculopapular rash, fever and respiratory symptoms caused by a single stranded RNA virus of the family of Paramyxoviridae and the genus of Morbilliviruses. Here progress in clinical case management is described.

Published in **Conn's Current Therapy. Rakel and Bope, Saunders Elsevier p 143-144, 2007. Invited Book Chapter**

Synthesis of 4-[2-Amino-ethyl(nitrosamino)]-1-pyridin-3-yl-butan-1-one, a new NNK hapten for the induction of N-nitrosamine specific antibodies

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4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) is one of the most abundant and potent pro-carcinogens in tobacco smoke. In order to induce a strong and substained antibody response against NNK we developed a functionalized derivative that closely mimicked its structural features in particular the pyridloxobutyl moiety, the adjacent ketone and the N-nitrosamino-group. This hapten was conjugated via a C_2 linker to the highly immunogenic diphteria toxoid licensed as a vaccine in humans to induce polyclonal and monoclonal antibodies.

Both P9D5 and P7H3 as well as the polyclonal antibodies reacted strongly with NNK (IC_{50} = 80µM or 160µM) and NNAL (IC_{50} = 29µM or 93µM) and to a lesser extend with some of the metabolites of NNK. Interestingly, the mAbs did not react with the metabolites of the detoxification pathways such as NNK-N-Oxide and NNAL-N-Oxide (IC_{50} > 512µM). Therefore such antibodies detect NNK and NNAL and may have the potential to modulate their redistribution in vivo, perhaps alleviating detrimental effects of smoking.

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Proteomic analysis of the cortisol-mediated stress response in THP-1 monocytes using DIGE technology

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The glucocorticoid (GC) cortisol, the main mediator of the hypothalamic pituitary adrenal axis, has many implications in metabolism, stress response and the immune system. Its function is mediated via binding to the glucocorticoid receptor (GR), a member of the superfamily of ligand activated nuclear hormone receptors. Subsequent actions result from receptor binding as a transcription factor to glucocorticoid response elements (GREs). By applying 2D gel electrophoresis with DIGE technology to study the effects of cortisol on the human THP-1 monocytic cell line, a total of 28 cortisol modulated proteins were identified belonging to five functional groups: cytoskeleton (8), chaperones (9), immune response (4), metabolism (3), and transcription/ translation (4). All corresponding genes were screened for putative glucocorticoid response elements (GREs) in their +10 kb/-0.2 kb promoter regions including all alternative promoters available within the Database for Transcription Start Sites (DBTSS). FKBP51, known to be induced by cortisol was identified as the strongest differentially expressed protein and contains the highest number of strict GREs. Genomic analysis of five alternative FKBP5 promoter regions suggests GC inducibility of all transcripts. Additionally, proteomics (2D-DIGE and 2D-immuno-blotting) revealed the existence of numerous FKBP51 isoforms, which were previously described. To our knowledge this is the first proteomic study which addresses the effects of cortisol on immune cells. FKBP51 isoforms found on the gel map could be linked to alternative promoter usage on the genetic level, successfully correlating both the specific proteomic and genomic advantages.

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Validation of a solid phase-bound steroid scaffold for the synthesis of novel cyclic peptidosteroids

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The current article reports on the synthesis of a new type of cyclic peptidosteroid, where a bile acid-based scaffold was used for the conformational restriction of a loop-like peptide. Convergent coupling of two tetrapeptides to the non-peptidic steroidal entity was carried out once in the classical C-to-N and once in the non-classical N-to-C direction. Peptide backbone cyclisation was then carried out, giving rise to a ring size equivalent to approximately twelve amino acids. This type of construct will be used in the development of a peptide vaccine against measles.

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Central African Republic is part of the West-African hepatitis B virus genotype E crescent

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Background: Recent studies have shown that Hepatitis B virus (HBV) genotype E predominates in a vast crescent in West-.Africa spanning from Senegal to Angola.

Objectives: To determine whether HBV strains in the Central African Republic (RCA) belong predominately to the homogeneous West-African genotype E or whether they are more closely related to genotypes found in East Africa.

Study Design: Serum samples were randomly collected from 196 patients admitted with symptoms of acute or chronic hepatitis to the Central Hospital in Bangui. Thirty complete and 36 partial sequences of HBV strains were obtained.

Results: 94 % (62/66) of the strains belonged to genotype E, while genotype A1, most closely related to a strain from Tanzania and genotype D were detected in only one and three samples, respectively. One strain presented a recombination between the S and X gene of a genotype E precursor and a partial PreC/C gene of a genotype D precursor.

Conclusions: Genotype E is predominant in RCA with little overlap with genotypes from Eastern Africa, extending the West-African HBV genotype E crescent further to the East.

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Hepatitis B virus genotype E surface antigen detection with different immunoassays and diagnostic impact of mutations in the preS/S gene

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Background. The major neutralizing epitope, the "a" determinant of the hepatitis B virus (HBV) genotype E surface antigen (HBsAg) is most divergent from that of genotype A, which is used for commercially available HBV reagents. Objectives. Evaluating the performance of the latest generation of detection assays with respect to genotype E HBsAg. Study Design. Three commercial assays were evaluated using sera from 200 Nigerian patients compared to the preS/S sequence of DNA positive samples. Results. 61 and 103 of 200 samples gave concordant positive and negative results between the three HBsAg assays. 35 samples with discordant results were confirmed negative by neutralization. One assay showed a particularly high rate of false positives (29 of 35), negative in the other two tests. DNA positive samples with reduced HBsAg detection signals (<75% of average) revealed several mutations, mostly outside the a-determinant, possibly interfering with the capturing antibodies of the assays. Several of these are found normally in genotype A and only exceptionally in genotype E. Conclusions. All three as-

says showed comparable sensitivities for genotype E HBsAg detection (98.4 % - 100 %) but differed considerably in specificity (84 % - 99 %). Differences in signal intensity were probably due to mutations in the preS/S gene some suggesting a positive genotype E to A detection bias.

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Adhesion molecules and cytokine expression in fibromyalgia patients: increased L-selectin on monocytes and neutrophils

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Objectives: The aim of the present study was to investigate possible abnormalities in the expression of adhesion molecules and cytokines in fibromyalgia (FM) patients, at basal conditions and after administration of dexamethasone (DEX). Methods: Expression of CD11a, CD11b, CD49d and CD62L (L-selectin) on leukocytes was analysed by flow cytometry and the concentration of soluble adhesion molecules, sICAM-1, sVCAM-1 and L-selectin, was measured by ELISA. T cell activation and intracellular IFN-γ expression were assessed by flow cytometry, after Staphylococcus aureus enterotoxin B (SEB) stimulation. Cytokine levels in PHA-stimulated cell culture supernatants were measured using a biochip array. Results: Differences in group response to DEX treatment were observed in particular in CD11b on NK cells, and L-selectin was elevated on monocytes and neutrophils of FM patients. The expression of other surface and soluble adhesion molecules was not different between FM patients and healthy controls. T cell activation assessed by the expression of the CD69 and IFN-γ expression by CD4 and CD8 T cells were normal in the patients. A tendency to lower IL-4 levels was observed but differences in cytokine levels between FM patients and healthy controls were not significant. Conclusions: The results from this study may be an indication of altered adhesion and recruitment of cells of the innate immune system to inflammatory sites of FM patients, at baseline and under stress. Thus, higher susceptibility for inflammation could contribute to FM symptoms.

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Molecular and antigenic evolution and geographical spread of H5N1 highly pathogenic avian influenza viruses in western Africa

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Nigeria was the first country in Africa to report highly pathogenic avian influenza (HPAI) caused by H5N1 virus. The virus was first detected in the North from where it seemed to have spread to other regions of the country. Since then 7 other African countries have reported HPAI H5N1 infections. Here we report the comparison of full-length genomic sequences of H5N1 isolates from commercial chickens from 7 farms in Nigeria, a family chicken and a hooded vulture in Burkina Faso, with those of earlier HPAI H5N1 outbreaks worldwide. 5 Nigerian farms strains suggested a spread of the virus within the country too. Nigerian SO, BA and Kaduna farms were infected by 3 viruses independently introduced in the country, while BA farm strains could have spread to FA, IF, OD and AB farms. In Burkina Faso a single strain could have originated from Northern Nigeria and spread to several places and hosts in the country. The Western African sub-lineages clearly cluster within the Western Asian/Russian/European lineage and are distinct from the Southeast Asian lineages.

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Co-circulation of multiple rubella virus strains in Belarus forming novel genetic groups within clade 1

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Although the WHO recommends a comprehensive genetic characterization, little is known about circulating strains and genotypes of Rubella virus (RV) for many European countries. Studies investigating the genetic diversity of a sizeable number of strains from a certain location are rare. We present here the first molecular characterisation of isolates from Belarus. Throat swab and urine samples were collected between 2004 and 2005 from patients presenting in 2 infectious disease hospitals and 3 outpatient clinics in and around Minsk. In total 14 isolates were obtained from this clinical material. The E1 gene sequence of our isolates exhibited a remarkably high diversity. Phylogenetic analysis showed that three distinct groups of RV strains co-circulated. One group of isolates was assigned to genotype 1E, whereas the other two did not group with any of the recognized genotypes, but with a strain belonging to the provisional genotype 1g. Detailed analysis showed that the group of 1g strains contains 4 subgroups, one of which might represent a putative new provisional genotype of clade 1. Our findings show an unexpected diversity of new groups of strains with limited variability suggesting independent introductory events. As currently there seem to be misattributions of strains to genotypes and unclear phylogenetic relationships, criteria for genotyping of RV should be further clarified.

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Genetic characterization of HPAI (H5N1) viruses from poultry and wild vultures, Burkina Faso

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On February 7th 2006, the first African outbreak of highly pathogenic avian influenza (HPAI) H5N1 virus was reported from a farm in Kaduna state, Northern Nigeria. Since then, seven other African countries including Niger, Egypt, Cameroon, Burkina Faso, Ivory Coast, Sudan and Djibouti have officially reported HPAI H5N1 in poultry farms to the World Organization for Animal Health (OIE). On April 3rd H5N1 was first confirmed in Burkina Faso. Here we analysed genetically H5N1 viruses from Burkina Faso poultry and the first gene sequences obtained from African wild birds, hooded vultures (Necrosyrtes monachus).

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World Health Organization. anonymus. Update of standard nomenclature for wild-type rubella viruses

Virological surveillance data on rubella viruses are used to track progress towards the goal of eliminating rubella, to help with case classification and to document transmission pathways.1 In 2004, representatives from WHO's global measles and rubella laboratory network met to develop a standardized nomenclature for wild-type rubella viruses; they described 7 recognized genotypes and 3 provisional genotypes of wild-type rubella viruses.2

The current update of the nomenclature is presented here; it describes 3 additional provisional genotypes and the upgrading of 2 provisional genotypes, to give 9 recognized genotypes (1B, 1C, 1D, 1E, 1F, 1G, 2A, 2B, 2C) and 4 provisional genotypes (1a, 1h, 1i, and 1j) (Fig. 1). The numbers refer to large distantly related groups of viruses designated as clade 1 and clade 2; letters represent genotypic groups within the clades with lower case letters representing provisional genotypes.

The nomenclature for wild-type rubella viruses facilitates virological surveillance by defining standard methods for the genetic characterization and naming of these viruses. The nomenclature system must be able to accommodate the discovery of new rubella viruses, the evolution of known viruses and periodic strain displacement. This flexibility is primarily obtained through the use of provisional genotype designations for virus groups that are small but diverse, for those that do not have the required reference viruses or for those where the relationship with other genotypes is unclear. The nomenclature is based on nucleotide sequences from recognized and provisional genotypes of rubella viruses.

Information about the global distribution of wild-type rubella viruses has been published.1 This update of the nomenclature provides a summary of the classification of rubella viruses including those that have been identified and analysed since the report of the first meeting in 2004. The genotypes of some viruses described in that report have now been clarified by comparing their nucleotide sequences with the larger current data-set of sequences.3

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Modulation of behavior and NMDA-R 1 gene mRNA expression in adult female mice after sub-acute administration of benzo(a)pyrene

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The behavioral performances of adult mice exposed to sub-acute doses of benzo(a)pyrene (B(a)P) were monitored in tests related to learning and memory (Y maze and Morris water maze), locomotor activity (open-field test) and motor coordination (Locotronic apparatus). At low doses (0.02 and 0.2 mg/kg), B(a)P impaired short-term learning and spatial memory performance in the Y maze and in the Morris water maze tests. Surprisingly, in the Y maze, the performances of animals exposed to the highest dose of B(a)P (200 mg/kg) were quite similar to those of control animals. Hyperactivity observed in both tests at this dose and attributed to an anxiolytic-like effect of B(a)P may have blurred the learning deficit in these mice faced with a new situation. These deficits seem to be unrelated to motor impairments because B(a)P had no effect on locomotor activity and motor coordination. We demonstrated that sub-acute exposure to B(a)P in adult mice also modulates gene expression of NMDA-R1 subunit in brain areas highly involved in cognitive function like the hippocampus, suggesting a relationship between the expression of functional NMDA-R1 mRNA, impairment of short term and spatial memory and the B(a)P exposure levels.

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Determination of Hepatitis B Virus Genotype by Flow-through Reverse Dot Blot

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Background: Infections by different hepatitis B virus (HBV) genotypes tend to differ in their clinical outcome and in response to therapy. A number of methods have been developed to determine the genotype of the virus, but most of them are relatively time-consuming and expensive. Moreover, the results of some methods are influenced by single nucleotide mutations.

Objectives: To develop a novel HBV genotyping method that is based on an improved reverse dot blot method using the principle of "flow-through hybridization" and the result of which is insensitive to single nucleotide mutations.

Study Design: The flow through reverse dot blot (FT-RDB) method was developed using DNA of different HBV genotypes. HBV sequences from Genebank were used to design primers and probes. The specificity and sensitivity of the method was evaluated with clinical samples of which the HBV viral load was quantified by real-time PCR. The results of the method were compared with multiplex PCR and sequencing. Another 59 clinical samples were used to test the clinical application of the method.

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Genotyping of recent Measles Virus strains from Russia and Vietnam by nucleotide specific multiplex PCR

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The nucleoprotein genes of 49 measles virus strains circulating in Russia between 2000 and 2006 and in Vietnam in 2003 were analysed by genotype-specific PCR and the results were compared with their sequences. The sequences revealed the presence of genotypes H1 and H2 in the Centre (Nha Trang) and the North (Hanoi) of Vietnam, respectively. The relative diversity of the H2 strains suggested an endemic circulation of these viruses in the capital. In contrast genotype H1 strains from Nha Trang were genetically homogenous, which may indicate a recent importation. The strains obtained from 12 different regions of the Russian Federation were assigned to the genotypes H1, D4 and D6. Most strains (81.4%) were correctly genotyped by a multiplex PCR method, described earlier by us, which was sensitive to genotype specific mutations. Ambiguous or negative results for some clade H and genotype D6 strains were due to point mutations in the type-specific primer binding sites. After exchanging a single nucleotide in both the clade H and the genotype D6 specific primers, all strains were correctly assigned to their genotype. A simplified procedure for use in Vietnam was developed to distinguish directly between genotypes H1 and H2 and any non-H genotype. These results demonstrate that our multiplex PCR method can be easily adapted to new sequence variants or specific epidemiological situations, and thus be very useful for rapid genotyping of large numbers of samples even in laboratories which do not have sequencing facilities.

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Evaluation of vaccine cold chain system and potency status of measles vaccine administered in Lagos State, Nigeria

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The National (level 1), State (L2), and Local government vaccine cold stores (L3) as well as some vaccination centres (L4) were physically inspected in Lagos State, Nigeria and the potency of the live-attenuated measles vaccine was tested. Both the L1 and L2 storage facilities were formally adequately equipped and maintained. This was also reflected in the potency of the vaccines. However, many vaccines at L1 were within weeks from expiration. Considerable problems with refrigeration and delayed forwarding became apparent at level L3 causing loss in potency both at L3 and L4: although, all L4 stores check-listed met all the EPI/NPI accreditation criteria, ¾ of the vaccines were sub-potent and this situation did not improve over the three year study period (1996-98). Time to expiration did not seem to be the main cause of loss of potency but rather poor and delayed handling. It is recommended that vaccines are moved more rapidly through the system and used well before expiration. Because of frequent power failures despite standby generators, we further recommend to include in the WHO criteria, book-keeping of periods of power failures, running time of generators and a complete recording of fuel consumption. Attitudes among vaccinating staff and handling of vaccines should also be improved by continued training.

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A new transcript splice variant of the human glucocorticoid receptor: Identification and tissue distribution of hGRΔ313-338, an alternative exon 2 transactivation domain isoform

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All human glucocorticoid receptor isoforms (hGR) are encoded by the NR3C1 gene consisting of 7 core exons (exons 2-8) common to all protein isoforms. The gene has two major exon 8-9 splice variants and a 5'-UTR consisting of 11 alternative splice variants. The N-terminal region of the hGR includes a tau-1 transactivation domain that interacts with proteins in the basal transcriptional apparatus, including the TATA box-binding protein. Here, we report the existence and the tissue distribution of a novel splice variant, hGRΔ313-338, with a 26 residue (78 bp) deletion in this N-terminal region encoded by exon 2, between amino acids 313 and 338. The hGRΔ313-338 observed at the mRNA level represents a transcript variant encoding a smaller protein isoform detected by WB with a predicted deletion between the tau-1 domain and the DNA binding domain (DBD) encoded by exons 3 and 4. Previous studies in transgenic mice showed that the removal of the entire exon 2 covering both the tau-1 transactivation domain and our deleted region produced a functional receptor albeit with an altered glucocorticoid-induced gene transcription pattern. Interestingly, the deleted residues show a number of potential phosphorylation sites including serine 317, known to be phosphorylated. It is thought that phosphorylation plays an important role in transactivation action of hGR. Thus, we hypothesise that hGRΔ313-338 represents a hGR isoform with an altered glucocorticoid-induced transactivation profile.

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Nuclear receptors in human immune cells: expression and correlations

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Nuclear receptors are key modulators of gene transcription. Their activity is ligand induced and modulates a large variety of tissue-specific cellular functions. However, for many nuclear receptors little is known about their role in cells of the immune system. In this study, expression patterns and distribution of 24 nuclear receptors were investigated in human peripheral blood mononuclear cells. We provide the first evidence of the expression of the 12 receptors CAR, CoupTFα, CoupTFβ, FXR, GCNF, HNF4α, PPARβ/δ, PXR, RevErbβ, TR2, TR4 and TLX in highly purified CD4, CD8, CD19, CD14 cells. The expression profile of RevErbα and LXRα previously observed in B cell and macrophages respectively has been extended to CD4, CD8 and CD14 cells. Except for RARβ, which was absence in any of the cells tested, our results suggest an almost ubiquitous expression of the nuclear receptors in the different cell lineages of the immune system. The expression of CAR, CoupTFα, FXR was also confirmed at a protein level and despite inconspicuous mRNA levels of HNF4α, only low levels of this receptor were detectable in the nuclear fraction of PBMCs. Expression of the latter receptors was mostly only a fraction (4-20%) of their expression in the thyroid, the adrenal gland, the lung or subcutaneous fat tissue. The Spearman rank order correlation test was performed to examine the correlation in expression between individual nuclear receptor pairs in the four cell types for several donors. Distinct correlation patterns were observed between receptor pairs in the individual cell types. In CD4 T cells four NR, GCNF, PPARγ, PPARα7 and RevErbβ perfectly correlated with each other ($P \leq 0.0167$). In the other cell types correlations between NR pairs were more diverse, but also statistically highly significant. Interestingly, the relative expression level of a number of receptor pairs ranked identical or similar in at least 3 (CoupTFα and PPARβ/δ, CoupTFβ and HNF4α as well as RORβ and PXR) or 4 cell types (CoupTFα and CoupTFβ, PPARγ and RevErbβ). Despite the variability of NR expression in immune cells, these results suggest that some of the NR may be co-regulated in human immune cells.

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Reducing global disease burden of measles and rubella: Report of the WHO Steering Committee on research related to measles and rubella vaccines and vaccination, 2005

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The WHO Steering Committee reviewed and evaluated the progress towards global control of measles and rubella and provided guidelines for future research activities concerning both diseases during its last meeting in New Delhi, in April 2005. Global measles vaccination coverage increased from 71% in 1999 to 76% in 2004 and indigenous transmission was interrupted or kept at very low levels in many countries. However, Africa and Southeast Asia continue to experience endemic transmission and high mortality rates, despite a global mortality reduction of 39% between 1999 and 2003. On the basis of reports from countries with continued indigenous measles virus transmission, future control strategies as well as advantages and potential drawbacks of global measles eradication were discussed. Similarly the burden of rubella and congenital rubella syndrome (CRS) as well as the cost-effectiveness of rubella vaccination was assessed using different methods in several countries without vaccination programs. As measles and rubella viruses continue to circulate surveillance and control strategies need further optimisation. RT-PCR was considered as an alternative method for laboratory diagnosis of CRS. The value of dried blood spots and oral fluid as alternative samples for measles and rubella IgG and IgM detection and genotype determination was evaluated. However further validation of these methods in different settings is required before their routine use can be recommended.

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L'étude de l'épidémiologie moléculaire de H5N1 hautement pathogène au Nigéria indique que plusieurs virus distincts y ont été introduits

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Le Nigéria est le premier pays africain à annoncer être touché par une souche hautement pathogène du virus de la grippe aviaire H5N1. Le virus a tout d'abord été détecté dans le Nord et il est maintenant signalé dans la moitié des états fédéraux nigérians. Nous comparons ici des séquences génétiques d'isolats de H5N1 provenant de 2 élevages dans l'état de Lagos avec un isolat de la première épidémie signalée dans l'état de Kaduna. Malgré la proximité des 2 élevages dans l'état de Lagos, ils ont été infectés par des virus de 2 lignées différentes, toutes deux également distinctes de celle observée dans le Nord (état de Kaduna). Ces données appuient la thèse de l'introduction indépendante de trois lignées de H5N1. Cependant la voie d'introduction des virus reste obscure puisqu'elle peut être expliquée par l'arrivée d'oiseaux migrateurs tout comme par importations commerciales indépendantes.

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Avian flu: multiple introductions of H5N1 in Nigeria

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As the avian influenza virus H5N1 swept from Asia across Russia to Europe, Nigeria was the first country in Africa to report this highly pathogenic avian influenza (HPAI) virus. Here we report the analysis of H5N1 sequences from two different farms in Lagos State, supporting the independent introduction of three H5N1 lineages along routes that coincide with migratory bird flyways but do not exclude independent trade imports.

Published in **Nature 442, 37, 2006**

H5N1, From the front lines: Nigeria, CP Muller

D. Butler

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Identical Genotype B3 Sequences from Measles Patients in 4 Countries, 2005

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The identification of measles virus genotypes from outbreaks and sporadic cases is an important aid in epidemiologic investigations and evaluation of control activities following introduction of virus into countries that have measles elimination programs. Many of the 23 known genotypes have geographical associations to countries or regions with endemic measles. Measles genotypes in clade B (B1, B2, B3) are associated with endemic circulation of measles in various countries in sub-Saharan Africa.

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Enhanced laboratory surveillance of group III coronaviruses in life poultry markets in Guangdong province, China, after the SARS outbreak

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One hundred and seven chickens or silky chickens were tested for infectious bronchitis virus between August 2003 and December 2005 in Guangdong and Hunan Chinese provinces, from which SARS coronavirus has initially emerged. IBV was detected in 82 birds (prevalence: 77%). Limiting the IBV detection PCR to tracheal or cloacal swabs would have led to a considerable underestimation of virus prevalence of 50 to 66% only. 15 sequences of 362 bp of the spike 1 gene (S1) were obtained. 13 strains clustered with Chinese genotype IV strains, which were recently reported in South China too. Genotype IV also showed the larger evolutionary distances in comparison to other Chinese genotypes. IBV/CK(T)/GD.CH/05-04/3587 strain clustered with genotype III virus, showing that genotype III continues to circulate in Guangdong province at least. A vaccine strain was probably detected in a bird as IBV/CK(C)/HN.CH/05-06/2904 was identical to H120 and H52 vaccines which are commonly used in Chinese poultry farms. It is nevertheless not likely that the IBV strains which could not be sequenced were vaccine strains: since both detection and sequencing PCRs were equally sensitive for the vaccine strain, sequencing would rather overestimate vaccine strains than wild-type variants. Our results suggest that at life-bird markets almost all birds carry wild-type IBV and that these markets may be an important and so far underestimated source of infection for IBV.

Published in **Proceedings of the 5th International Symposium on Avian Corona- and Pneumovirus, Rauischholzhausen, Germany 132-140, 2006**

World Health Organization. anonymus. Global distribution of measles and rubella genotypes – update

The WHO Measles and Rubella laboratory Network (LabNet) has been established to provide a standardized testing and reporting structure with a global quality assurance programme. The LabNet has grown to include approximately 700 labs in 166 countries confirming measles and rubella cases by IgM testing. Besides serologic testing, another important function of the network is to support the genetic characterization of currently circulating measles and rubella viruses. Virological surveillance data, when analysed in conjunction with standard epidemiologic data, can help to document viral transmission pathways and aid in case classification, thus enhancing control programs. Molecular epidemiologic data often provides important information for documenting the elimination of endemic transmission of measles or rubella.

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The genetic characterization of wild-type measles virus strains, isolated in the Russian Federation in 2003 - 2005

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Tissue specific glucocorticoid receptor expression, a role for alternative first exon usage?

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The CpG island upstream of the GR is highly structured and conserved at least in all the animal species that have been investigated. Sequence alignment of these CpG islands shows interspecies homology ranging from 64 to 99%. This 3.1 kb CpG rich region upstream of the GR exon 2 encodes 5' untranslated mRNA regions. These CpG rich regions are organised into multiple first exons and, as we and others have postulated, each with its own promoter region. Alternative mRNA transcript variants are obtained by the splicing of these alternative first exons to a common acceptor site in the second exon of the GR. Exon 2 contains an in-frame stop codon immediately upstream of the ATG start codon to ensure that this 5' heterogeneity remains untranslated, and that the sequence and structure of the GR is unaffected.

Tissue specific differential usage of exon 1s has been observed in a range of human tissues, and to a lesser extent in the rat and mouse. The GR expression level is tightly controlled within each tissue or cell type at baseline and upon stimulation. We suggest that no single promoter region may be capable of containing all the necessary promoter elements and yet preserve the necessary proximity to the transcription initiation site to produce such a plethora of responses. Thus we further suggest that alternative first exons each under the control of specific transcription factors control both the tissue specific GR expression and are involved in the tissue specific GR transcriptional response to stimulation. Spreading the necessary promoter elements over multiple promoter regions, each with an associated alternative transcription initiation site would appear to vastly increase the capacity for transcriptional control of GR.

Published in **Biochemical Pharmacology 72, 1529-37, 2006**

Seroprevalence of Avian Influenza Virus, Infectious Bronchitis Virus, Reovirus, Avian Pneumovirus, Infectious Laryngotracheitis Virus, and Avian Leukosis Virus in Nigerian Poultry

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Eight poultry farms in Nigeria including chickens from 9 breeder, 14 broiler, 28 pullet, 11 layer, and 3 cockerel flocks were tested for antibody seroprevalence to the following poultry viruses of potential economic importance: infectious bronchitis virus (IBV), avian reovirus, avian pneumovirus (APV), infectious laryngotracheitis virus (ILTV), avian influenza virus (AIV), and avian leukosis virus (ALV). Serum samples were collected between 1999 and 2004 and were tested for antibodies using commercial ELISA kits. Seroprevalence was very high for IBV (84%), intermediate for reovirus (41%), APV (40%) and ILTV (20%) and very low for ALV (<5%) antibodies. By commercial ELISA the seroprevalence of antibodies against AIV was in some flocks up to 63%. However, more specific assays did not confirm AIV antibodies indicating that all flocks tested were free of avian influenza antibodies. Birds seemed to be first infected by IBV (at about 7 weeks of age), then by reovirus at 12 weeks, before they become infected by APV (week 25) and ILTV (week 30). This is the first report of serological evidence of the above viruses in West Africa. Further studies are necessary to assess economic losses due to these avian viruses and the cost-benefit of countermeasures.

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Phylogenetic analysis of the precore/core gene of hepatitis B genotypes E and A in West-Africa: New subtypes, mixed infections and recombinations

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122 new hepatitis B virus (HBV) preC/C sequences and 3 complete genomes from three major countries in West-Africa were analysed. The majority of sequences were of genotype E and the only other genotype found was genotype A. Although for genotype E sequences the genetic diversity of the preC/C gene was about 2 – 3 times higher than the diversity of the preS/S, it was still considerably lower than for genotype A sequences. The HBV/E preC/C gene was most closely related to D1 and D2 sequences. Evidence of recombination was found in two strains that were genotype A in the preS/S gene and E in the preC/C gene. The genotype A strains from Cameroon, Mali and Nigeria could be phylogenetically divided into 3 subtypes, A3 and 2 new subtypes, tentatively designated A4 and A5. Each subtype presented a genetic diversity of 2.19 % to 3.85 % and inter-subtype distances of 4.47 % to 5.97 %. Interestingly, one sample from Nigeria showed evidence of a triple recombination of genotype E/D and A, separated by a genotype G specific insert of 36 bp. Of 110 patients, 19 (17.3 %) showed a co-infection of genotypes A and E, mostly in HIV-positive children from Cameroon. Thus in Cameroon, where both genotypes co-exist, 37 % of all individuals tested have mixed infections. The low genetic variability in the preC/C gene of genotype E supports our previous speculation about a relatively short evolutionary history of this genotype, in contrast to the subtype-rich African genotype A strains.

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Potential of NanoSIMS for Life Sciences

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For many biologists, material science belongs to the arcane domain of physics. While several surface analysis techniques such as atomic force microscopy (AFM) or scanning electron microscopy (SEM) have been successfully used in life sciences, others are less known outside the material science community. Secondary ion mass spectroscopy (SIMS) is one of those techniques that is still largely unknown to biologists even after almost forty years of existence, partially because of its complexity and difficulties of communication between physics and biology. Nevertheless, the last decades have seen a number of applications in biology, suggesting that SIMS may also be useful beyond material sciences.

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Waning antibodies in measles and rubella vaccinees-a longitudinal study

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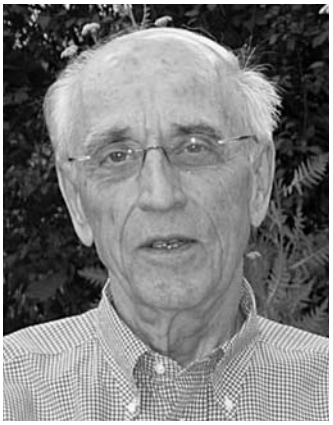
The evolution of measles- and rubella-specific serum IgG was followed in a longitudinal study in 224 young adolescent vaccinees, with or without boost vaccination before or during the 6.8-year observation period. Antibody titres were monitored by enzyme immune assay (Enzygnost®, Dade-Behring). After revaccination (2nd dose) rubella seropositivity rate increased from 93.8% to 100%, whereas measles seroprevalence (about 90%) did not significantly change between the paired sera. Significantly higher IgG (>3-fold) in the second serum of 5.2% (measles) and 7.8% (rubella) of participants with low antibodies (measles: <1500mIU; rubella <40IU) in first serum, suggest a secondary immune response (SIR) during the study period, only partially explained by revaccination. Excluding individuals with SIR, minimal annual antibody decay rates of –2.9% (CI: -0.7 to -4.8%) for rubella and -1.6% (CI: -0.1 to -3 %) for measles were determined in participants with single dose vaccination. Thus two-dose vaccination was adequate to protect women from rubella infection at least during childbearing age. Similarly only few individuals may become seronegative for measles again after successful vaccination due to minimal waning of low antibody levels (<1500 mIU). However, as a result of a more rapid decay of high-titre (>1500mIU) antibodies (-2.4%/year), many vaccinees may eventually become susceptible to vaccine-modified measles and consequently complicate measles control strategies.

Published in **Vaccine 24, 2594-601, 2006.**

In Memoriam Marcel LEMMER

(1925 - 2007)



Noël 2007, le 24 décembre. Ce jour-là, pourtant jour de joie et de lumière, s'est éteint notre ami et confrère Marcel Lemmer, vaincu par un mal impitoyable.

Relater sa biographie, c'est commencer de façon des plus banales: naissance à Esch-sur-Alzette, le 10 juin 1925, école primaire à Esch, études secondaires à Echternach.

Mais voilà que survient la guerre, et Marcel est enrôlé de force par les Allemands, envoyé à l'Est, blessé et soigné pendant plusieurs mois dans un hôpital militaire. Il sortira vivant de la tourmente, mais il en restera marqué pour le reste de sa vie.

Après ses études de médecine à Bruxelles, il s'engage à Paris au service des professeurs Bricaire et de Gennes et commence à se passionner pour l'endocrinologie qui deviendra avec la médecine interne sa spécialité. Aussi sera-t-il le premier à pratiquer cette spécialité au Luxembourg.

Installé dans la capitale il va faire partie de l'équipe médicale de la clinique d'Eich. C'est là qu'il va faire preuve de l'étendue de ses connaissances et de ses qualités de médecin. Avec obstination, voire même une certaine sévérité, il s'attaquera entre autre aux problèmes du diabète et de l'obésité. Problèmes, on le sait, ingrats, s'il en est.

Paraissant toujours pressé, parfois soucieux, Marcel n'en appréciait pas moins l'humour et les rencontres avec ses confrères. Souvent c'était lui qui élevait le niveau des débats lors des 'pauses-café' à la clinique, et souvent le sujet en était l'Histoire qu'il connaissait parfaitement. Etant bon dessinateur, il s'intéressait tout naturellement à la peinture, et retournait volontiers à Paris pour y visiter musées et galeries. Paris et la France étaient d'ailleurs pour ainsi dire sa deuxième patrie.

Marcel Lemmer ne recherchait pas la gloire ni les honneurs. Il lui suffisait de connaître l'estime de ses confrères et de ses patients, l'affection de sa famille et l'attachement de ses amis.

Le docteur Lemmer va nous manquer.

Robert Faber

Calendrier des conférences et présentations

organisées par ou sous les auspices de la Société des Sciences Médicales 2008

22.02.08 Workshop: Devoir de mémoire, devoir d'oublier. Regards croisés de l'histoire et de la psychanalyse, organisé par le projet de recherche LUX-ID du Laboratoire d'histoire de l'Université du Luxembourg en collaboration avec Espace Analytique (Paris), la Société des Sciences Médicales ainsi que la Société de Neurologie, de Psychiatrie et de Psychothérapie (Luxembourg) à l'Université du Luxembourg, Limpertsberg

27.02.08 Conférence d'Allergologie par le Pr. D.A. Moneret-Vautrin, le Pr. G. Pauli et le Dr F. Hentges, organisée par la SSM, la Société Luxembourgeoise d'Allergie et d'Immunologie et le Laboratoire Ketterthill au Casino 2000, Mondorf.

05.03.08 Violence conjugale. Dépistage et prise en charge, organisée par Amnesty International, l'ALFORMEC et sous les auspices de la SSM à l'Université du Luxembourg, Limpertsberg

17.03.08 La Sphérocytose Héréditaire par le Dr ès Sc. Dolphe Kutter, organisée par la Section des Sciences de l'Institut Grand-Ducal en coopération de l'ALFORMEC, de la Faculté des Sciences, de la Technologie et de la Communication de l' UNI.LU, de la SSM et de la Société des Naturalistes.

16.04.08 Zum Nutzen der Neurobiologie für die Diagnostik und Therapie stress-bezogener Gesundheitsstörungen von Prof. Dr. Dirk Hellhammer, dans le cadre de l'Assemblée Générale de la Société des Sciences Médicales, à l'Université du Luxembourg, Limpertsberg

05.05.08 Chimie des Sidérophores: vers de nouvelles molécules pour une santé … de fer par le Dr ès Sc. Gaëtan Mislin, Université Louis Pasteur de Strasbourg, organisée par la Section des Sciences de l'Institut Grand-Ducal en coopération de l'ALFORMEC, du Centre Culturel Français, de la Faculté des Sciences, de la Technologie et de la Communication de l'UNI.LU, de la SSM et de la Société des Naturalistes, à l'Université du Luxembourg, Limpertsberg

16.05.08 Journée Thématique International du CHL: Traitement des Tumeurs Secondaires du Foie par les Profs Awada, Bachelier, de Baere, Flamen, Maleux, Van Beers et les Drs Goergen, Jonard, Picard, Weber, au Grand Auditoire du CHL à Luxembourg.

25.05.08 Multiconférence «Toxicologie et Cancer» par le Prof. Pierre Seck, Madame Colette Keller-Didier, Nancy, le Prof. Bertrand Rihn, Nancy, le Prof. Denis Zmirou, Nancy, le Dr Elisabeth Luporsi, Nancy et le Dr Marc Diederich, Luxembourg, organisée par la Section des Sciences de l'Institut Grand-Ducal en coopération de l'Association Luxembourgeoise des Ingénieurs, de l'Association Luxembourgeoise des Ingénieurs-Architectes et Industriels, du Centre Culturel Français, de la Faculté des Sciences, de la Technologie et de la Communication de l'UNI.LU, de la Fondation Luxembourgeoise contre le Cancer, de la SSM et de la Société des Naturalistes au Grand Auditoire du CHL à Luxembourg.