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A MULTIDISCIPLINARY APPROACH TO NEUROSCIENCES

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MATTIOLI 1885



# CONFINIA CEPHALALGICA ET NEUROLOGICA

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Come i lettori avranno potuto notare *Confinia Cephalgica et Neurologica* è andata incontro negli ultimi numeri ad un “restyling” legato alla nuova linea editoriale che si intende promuovere.

Come si ricorderà la rivista è stata fondata ormai molti anni orsono dal professor Nappi con il nome di *Confinia Cephalgica*. La denominazione sottintendeva un interesse prevalente, o comunque prioritario, nel campo delle cefalee e del dolore.

Il termine “confinia” già allora indicava l’obiettivo della rivista di aprirsi a discipline di confine nell’ottica di integrare le conoscenze di vari campi di ricerca in una visione multidisciplinare degli argomenti trattati.

Successivamente il nome della rivista è diventato quello attuale, questo perché si è ritenuto di definire tra gli obiettivi primari quello di un dialogo allargato ai vari settori delle neuroscienze, fermo restando l’originale interesse per il campo delle cefalee e del dolore.

La rivista ha, quindi, ospitato sempre più frequentemente articoli riguardanti non solo le cefalee e le neuroscienze cliniche ma anche altre discipline ad esse relate, quali la neurofilosofia, la storia delle neuroscienze, eccetera.

La rivista, come è noto, pubblica articoli in tre lingue ovvero italiano inglese e spagnolo ed ha ospitato vari articoli nati da ricerche frutto di progetti di collaborazione internazionale in particolare tra Italia, Europa e Sudamerica.

Molto recentemente la rivista ha stabilito un legame con lo Special Interest Group “Neurophilosophy” della World Federation of Neurorehabilitation.

La Neuroriabilitazione, proprio per la sua vocazione olistica dettata dalla necessità di rapportarsi al paziente in quanto persona, considerando, quindi, sempre gli aspetti cognitivi, psicologici e socio-familiari, è disciplina particolarmente sensibile all’esigenza di superare i limiti legati ad un approccio strettamente settoriale e monospecialistico.

L’obiettivo primario del Gruppo resta quello di stabilire un collegamento multidisciplinare e multiculturale tra le neuroscienze cliniche e la filosofia, obiettivo che ci è parso pienamente in linea con la finalità della rivista, che è tesa ad esplorare sempre nuovi settori in un campo, quello delle neuroscienze, che come pochi altri ha avuto un prodigioso sviluppo nel corso degli ultimi decenni.

*Paolo Mazzarello, Franco Lucchese, Giorgio Sandrini*

# Jean-Martin Charcot (1825-1893) e la prima descrizione della “sindrome di Alice nel Paese delle Meraviglie”

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**Riassunto:** La “sindrome di Alice nel Paese delle Meraviglie” (SAPM) è un disturbo neurologico caratterizzato da dispercezioni visive o somestese frequentemente associate all’emicrania. La prima descrizione documentata di SAPM è quella di un paziente con macrosomatognosia ed emicrania con aura visitato da Jean-Martin Charcot (1825-1893) durante una lezione tenuta il 22 novembre 1887 alla Salpêtrière. Sebbene all’epoca questa condizione non fosse conosciuta, Jean-Martin Charcot cercò di inquadrare il complesso di sintomi riconducendoli all’emicrania con aura e all’epilessia sensitiva. Tale identificazione, sebbene discutibile, suggerì correttamente al neurologo la presenza di un disturbo dell’eccitabilità corticale di aree preposte all’elaborazione e alla percezione di stimoli sensitivi.

**Parole chiave:** Jean-Martin Charcot, storia della neurologia, SAPM, Salpêtrière

## JEAN-MARTIN CHARCOT (1825-1893) AND THE FIRST DESCRIPTION OF THE “ALICE IN WONDERLAND SYNDROME”

**Abstract:** The “Alice in Wonderland Syndrome” is a neurological disorder characterized by visual or somatic disturbances frequently associated with migraine. The first documented description of this syndrome is that of a patient with macrosomatognosia and migraine with aura evaluated by Jean-Martin Charcot (1825-1893) during a lecture given on November 22, 1887 at the Salpêtrière. Although at the time this condition was unknown, Charcot attributed the complex of symptoms to migraine with aura and sensory epilepsy. This diagnosis, although questionable, correctly suggested the presence of a cortical excitability disorder of areas responsible for processing and perception of sensory stimuli.

**Key words:** Jean-Martin Charcot, history of neurology, Alice in Wonderland syndrome, Salpêtrière

## JEAN-MARTIN CHARCOT (1825-1893) Y LA PRIMERA DESCRIPCIÓN DEL “SÍNDROME DE ALICIA EN EL PAÍS DE LAS MARAVILLAS”

**Resumen:** El “síndrome de Alicia en el país de las maravillas” es un trastorno neurológico caracterizado por alteraciones visuales o somáticas frecuentemente asociadas con la migraña. La primera descripción documentada de este síndrome es la de un paciente con macrosomatognosia y migraña con aura evaluada por Jean-Martin Charcot (1825-1893) durante una conferencia impartida el 22 de noviembre de 1887 en la Salpêtrière. Aunque en ese momento se desconocía esta condición, Charcot atribuyó el complejo de síntomas a migraña con aura y epilepsia sensorial. Este diagnóstico, aunque cuestionable, sugirió correctamente la presencia de un trastorno de excitabilidad cortical de áreas responsables del procesamiento y percepción de los estímulos sensoriales.

**Palabras Clave:** Jean-Martin Charcot, historia de la neurología, síndrome de Alicia en el país de las maravillas, Salpêtrière

## Introduzione

La “sindrome di Alice nel Paese delle Meraviglie” (SAPM; in Inglese: “Alice in Wonderland syndrome”) è un disturbo neurologico caratterizzato da una alterata percezione del proprio schema corporeo, eventualmente associata a sintomi dispercettivi visivi o somestesici (1, 2).

Dispercezioni visive (metamorfopsia) sono i sintomi più comuni (pur se poco specifici e assenti nella descrizione originaria) della SAPM, con micropsia e macropsia riportati nel 58.6% e 45.0% dei pazienti (1).

Tuttavia si possono verificare anche sintomi somestesici (considerati più specifici) e altri disturbi non visivi (1). Questa sindrome è considerata un’entità rara, sebbene fino al 30% degli adolescenti possa sperimentare, anche se saltuariamente e in maniera transitoria, sintomi riferibili ad essa (1).

L’eziologia di SAPM è estremamente eterogenea: in soggetti di età pediatrica e negli adolescenti la causa più frequente (21.6% dei casi) è l’encefalite infettiva, soprattutto da virus Epstein-Barr, mentre il 17.5% si associa all’emicrania; negli adulti l’emicrania è di gran lunga la condizione di più frequente riscontro (9.6% dei casi di SAPM) (1,3).

Recenti dati di neuroimaging suggeriscono che il carrefour temporo-parieto-occipitale sia una struttura chiave nella fisiopatologia di questo quadro clinico (4). La prognosi è strettamente dipendente dalla causa sottostante; i sintomi regrediscono completamente nel 46.7% dei casi, ma possono persistere nelle forme secondarie ad encefalite (1).

Il termine di SAPM, coniato nel 1955 dallo psichiatra inglese John Todd (1914–1987) (5,6), si rifà al titolo del famoso romanzo (1865) di Lewis Carroll, pseudonimo di Charles Lutwidge Dodgson (1832–1898). Nell’opera, Alice cambia dimensioni ben 12 volte, crescendo e rimpicciolendo (Figura 1), ed è stato ipotizzato che le esperienze vissute dalla protagonista riflettano alcuni sintomi sperimentati dallo stesso Carroll (7). Lo scrittore e matematico britannico soffriva infatti di attacchi di emicrania, spesso preceduti da fenomeni di aura visiva, che lo indussero a consultare il celebre oftalmologo William Bowman (1816–1892) (8). Secondo un’ipotesi alternativa, Carroll sarebbe stato a conoscenza delle proprietà allucinogene del



**Figura 1.** Illustrazione originale di Sir John Tenniel (1820–1914) tratta da “Alice’s Adventures in Wonderland” (Alice nel Paese delle Meraviglie, 1865). Immagine di pubblico dominio.

fungo *Amanita muscaria*, che avrebbe descritto nella sua opera (9).

Molti sintomi riferibili alla SAPM erano già stati riportati nella Letteratura medica prima del 1955, sia in trattati di neurologia generale (10) che in alcune descrizioni delle conseguenze cliniche di lesioni occipitali in soldati durante la Prima Guerra Mondiale (11).

In questo articolo presentiamo quella che è attualmente considerata la prima descrizione nota in Letteratura medica di sintomi riferibili a SAPM. Si tratta del resoconto clinico di un paziente visitato da Jean-Martin Charcot (1825–1893) durante una delle famose lezioni tenute alla Salpêtrière (12; 13).

Durante queste lezioni, che si svolgevano il martedì, il neurologo francese visitava alcuni pazienti di fronte ad un vasto uditorio, dando prova del suo acume diagnostico e della notevole abilità nel formulare precise diagnosi di localizzazione anatomica partendo dai dati anamnestici ed obiettivi. La trascrizione di queste lezioni, eseguite dai suoi allievi, sono un documento affascinante e dimostrano concretamente l’efficacia del metodo anatomo-clinico che Charcot contribuì a perfezionare e divulgare.

Le trascrizioni sono attualmente disponibili in due diverse edizioni. La prima, pubblicata nel 1887, è una litografia delle trascrizioni effettuate a mano da Edouard-Emmery Blin (1863–1930), Jean-Baptiste Charcot (1867–1936) ed Henri Colin (1860–1930) (12).

La seconda, risalente al 1892, è una versione a stampa (13). Anche se ad oggi non è stato condotto un approfondito studio comparativo tra le due versioni, esse differiscono a tratti in maniera considerevole, ed è difficile stabilire quale delle due sia la più attendibile (14).

Appare tuttavia probabile che la prima versione rifletta in maniera più accurata i dialoghi intercorsi fra Charcot e i suoi pazienti. La seconda infatti subì una revisione dei contenuti, espungendo o modificando in maniera rilevante parte del testo prima della pubblicazione a stampa, ma non è noto che parte ebbe Charcot in tale processo (15).

Riproponiamo di seguito una breve descrizione ed analisi del paziente con sintomi riferibili a SAPM visitato da Charcot, riportando in traduzione i passaggi più significativi del dialogo clinico tra i due, come presentato nella prima versione del testo (1887). Discutere questo caso clinico permette di sottolineare alcune peculiarità dei sintomi associati alla SAPM, apprezzando le peculiarità della metodologia di indagine clinica adottata dal grande maestro francese.

## Il caso clinico

Il secondo paziente visitato da Charcot nella lezione di martedì 22 novembre 1887 è un uomo di 37 anni, con una laurea in scienze («*licencié en sciences*»), che fino a 12 anni prima aveva goduto di buona salute. All'età di 23 anni aveva preso parte ad una spedizione di ricerca in Norvegia, durante la quale aveva trascorso una notte in mezzo alla neve; in seguito aveva avvertito dolori alle gambe e allo "stomaco" durati alcune settimane. Nei cinque o sei anni successivi non aveva sperimentato ulteriori problemi di salute.

Il paziente sintetizza in questo modo l'esordio e le caratteristiche del disturbo attuale:

«Nel 1879 o 1880 ho cominciato ad avvertire (degli episodi di) pesantezza alle braccia. Li ho ancora e cominciano dalle estremità delle dita. Le mie mani si gonfiano («*Mes mains gonflent*»), o almeno mi sembra che si gonfino, perché in realtà non è così. Successivamente avverto la medesima sensazione nelle braccia, poi nella spalla, poi nella gamba, e in tutta la parte destra del tronco. Anche i muscoli si gonfiano, la lingua

è dislocata violentemente nel lato destro (della bocca), ed è davvero così perché sento che tocca i denti.»

Charcot interrompe il Paziente per cercare di riorganizzare il materiale anamnastico in maniera più sistematica ed ordinata:

«*Charcot*: Ricostruiamo tutto questo. Il male di cui siete preda si manifesta per accessi (*accès*)?»

*Il Paziente*: Sì, per accessi separati da intervalli nei quali non ho disturbi, ma che tuttavia mi lasciano una difficoltà nel parlare che mi ha costretto a rinunciare all'insegnamento.

*Charcot*: Parliamo per prima cosa di questi episodi. Voi dite che in tali occasioni cominciate ad avvertire una sensazione particolare nella mano, ma senza che si manifestino dei movimenti: le dita non si muovono, il braccio non si muove. La sensazione che Voi provate consiste nel credere di sentire la Vostra mano come fosse più grande.

*Paziente*: La mano non è (realmente) più grande, ma tuttavia non riesco più a tenere in mano la penna! Non riesco più a scrivere.

*Charcot*: La seconda sensazione che sperimentate è nel tronco o nella gamba?

*Paziente*: Nella gamba: sento un formicolio al piede.»

A questo punto il neurologo francese si rivolge agli astanti e formula la diagnosi, inquadrando i sintomi riferiti dal Paziente in una epilessia parziale sensitiva:

«Notate bene questo aspetto. Si tratta di una forma di epilessia che non è molto ben conosciuta. Potete riscontrare questi fenomeni sotto forma di sintomi (che si presentano) in circostanze molto variegata, delle quali vi parlerò fra poco. Qui noi abbiamo a che fare con un tipo di epilessia parziale sensitiva. Dal momento che non si verifica alcun movimento, se non in misura secondaria, è la sensibilità ad essere coinvolta. Si può ipotizzare un'epilessia sensitivo-motoria, ma sono i fenomeni della sensibilità ad essere in primo piano.»

Dopo aver identificato ed isolato il sistema funzionale coinvolto nella sintomatologia del paziente, quello della sensibilità, Charcot procede chiedendo ulteriori dettagli per poter così organizzare ed ordinare i sintomi in una precisa successione temporale:

«*Charcot*: La sequenza abituale: braccio, gamba,

faccia?

*Paziente:* Sì.

*Charcot:* Per inciso, vi faccio notare che qui c'è una piccola anomalia: la sequenza dovrebbe infatti essere: braccio, faccia, gamba.

*Paziente:* La faccia è coinvolta quasi contemporaneamente alla gamba.

*Charcot:* Siete certo che la gamba non sia coinvolta per prima?

*Paziente:* Solitamente non è la gamba ad essere coinvolta per prima, ma la mano. Poi la gamba e la faccia, queste ultime quasi in contemporanea.

*Charcot:* In generale ecco (la sequenza con cui) si verificano i fenomeni: braccio, faccia e gamba. Potrebbe essere che il malato si sbaglia, dal momento che solitamente gli accessi cominciano con un intorpidimento della mano; questo primo fenomeno è seguito da un formicolio nel braccio che risale, o almeno dà l'impressione di risalire; la faccia è coinvolta successivamente, ma non del tutto.»

Successivamente, Charcot interroga il paziente sulla sensazione di intorpidimento della lingua, sottolineando come «vi siano aspetti in comune fra le epilessie motorie e le epilessie sensitive», e come nel caso in esame sia presente «una mescolanza di epilessia motoria e di epilessia sensitiva, ma i fenomeni dominanti sono soprattutto sensitivi». Dopo aver escluso un interessamento a carico della muscolatura della faccia, Charcot evidenzia come il paziente presenti, nel corso degli episodi clinici, un disturbo transitorio di tipo afasico, seguito da cefalea. Infine, il paziente riferisce di percepire nell'occhio destro, durante gli attacchi più intensi, «un'immagine luminosa, costituita inizialmente da raggi luminosi disposti attorno ad un cerchio scuro di 5 millimetri di diametro, poi da linee luminose a partenza dai raggi di luce, che danno origine ad un'immagine lunga 4 centimetri». Questo dato anamnestico consente a Charcot di presentare agli uditori le caratteristiche dello spettro di fortificazione tipico della *migraine ophthalmique*. In riferimento ai sintomi presentati dal paziente, egli sottolinea come in alcuni casi lo scotoma scintillante possa associarsi ad un intorpidimento della mano che risale a coinvolgere la faccia e la lingua, dando origine ad una afasia espressiva transitoria con parafasie semantiche, talora con alessia ed agrafia.

Charcot cela a fatica un certo disagio nell'inquadramento diagnostico dei sintomi presentati dal paziente. A tale proposito egli afferma: «Il malato che è davanti a noi ha lo scotoma, i dolori ed infine – come a coronamento dell'edificio – attacchi di epilessia parziale sensitiva». Eppure, alla domanda «Ebbene, che ha dunque il nostro malato?», Charcot risponde «sono costretto a dirvi che non lo so».

## Discussione

Questo caso clinico riporta la prima descrizione nota in Letteratura medica di sintomi riferibili a SAPM associata ad emicrania con aura. Il paziente presentava sintomi somestesici inquadabili come macrosomatognosia parziale, la sensazione che una o più parti del proprio corpo siano più grandi rispetto al normale. Nel caso in esame tali sintomi - riportati nel 7% dei casi di SAPM (1) - erano di pura natura somestesica, e non si associavano a macropsia o micropsia.

La concomitanza di sintomi somestesici e di altri imputabili all'aura emicranica può spiegare le difficoltà mostrate da Charcot nell'inquadramento semeiologico e nosografico del caso.

Per quanto riguarda l'interpretazione fisiopatologica e la correlazione anatomo-clinica dei sintomi presentati dal paziente, Charcot ipotizzò «un'irritazione molto lieve della corteccia, poiché là si trova la causa di queste epilessie parziali che a volte cominciano con gli arti superiori e a volte con la faccia, e la cui evoluzione clinica riflette il coinvolgimento di aree vicine (*et qui continuent leur évolution par action de voisinage*)» (12).

Non potendo tuttavia riscontrare nel paziente una sequenza nell'evoluzione temporale dei sintomi sensitivi paragonabile a quella attesa per i fenomeni motori di una epilessia parziale con marcia jacksoniana, Charcot concluse che «Tutto questo vale per le epilessie parziali motorie (in cui) vedete come la sequenza (di fenomeni) è sempre più o meno regolare; ma per quanto riguarda le forme sensitive ne siamo meno certi, perché l'esperienza non ci dice granché. Noi sappiamo solamente che le lesioni che si traducono in questi sintomi si trovano nella regione posteriore. Comprendete (quindi) perché l'epilessia sensitiva si trovi così spesso



associata all'epilessia motoria: perché entrambe hanno la loro sede in due regioni vicine» (12).

Al termine della sua valutazione il neurologo si era astenuto dal formulare una diagnosi precisa ed univoca. Tuttavia, egli aveva identificato i sintomi somestesici con quelli dell'epilessia sensitiva. Questo evidenzia come il grande maestro francese tendesse a ricondurre sintomi disparati ed inabituali a pattern nosografici ben noti e definiti. Tale atteggiamento di sistematizzazione (ed inevitabile semplificazione) consentiva a Charcot di creare ordine a partire da una presentazione clinica apparentemente caotica (16).

Come ricordato da Sigmund Freud (1856-1939), il maestro «Era solito osservare attentamente, più e più volte, le cose che non conosceva, rafforzando così l'impressione che ne aveva tratto: giorno per giorno, fino a che non gli si dischiudeva, all'improvviso, il loro intimo significato. Il caos apparente del continuo ritorno degli stessi sintomi gli si ordinava allora davanti agli occhi, ed ecco uscirne, caratterizzati dal nesso costante di determinati gruppi di sintomi, i nuovi quadri clinici; i casi limite, i "tipi", si lasciavano delineare in tutta la loro completezza con l'aiuto di una speciale schematizzazione, e partendo da questi tipi la visione si estendeva sulla lunga serie dei casi meno evidenti, le *formes frustes* che, iniziando da questo o da quel segno caratteristico di un dato tipo, sfumavano verso l'indeterminato. Questo genere di lavoro intellettuale, nel quale nessuno poteva essergli pari, Charcot lo chiamava "fare della nosografia" e ne era orgoglioso.» (17).

La diagnosi finale del paziente, riportata nel sommario della lezione, è quella di "*épilepsie sensorielle, migraine ophthalmique*". Sarebbe sin troppo facile criticare la diagnosi apparentemente semplicistica e, sulla base delle nostre conoscenze, errata (*absit iniuria verbis*) posta da Charcot: non si può certo rimproverare al neurologo francese di non essere riuscito ad identificare una serie di sintomi riferibili ad una sindrome non ancora descritta nella Letteratura medica! Tuttavia, l'esempio evidenziato dimostra come neppure il grande maestro fosse totalmente immune dal rischio di trarre alcune conclusioni distorte dal cosiddetto "bias di conferma" ("*confirmation bias*"), tendendo quindi a confermare conoscenze acquisite, anziché riconoscere di trovarsi di fronte a fenomeni non riconducibili ad entità cliniche già note. A tale proposito si segnala

come, già al momento di chiedere al paziente ulteriori dettagli in merito alla sua sintomatologia, Charcot avesse utilizzato il vocabolo "*accès*" (accesso, parossismo), termine solitamente riservato alle crisi epilettiche, invece di "*attaque*", impiegato per indicare altri fenomeni parossistici non-epilettici o isterici (14).

## Conclusioni

L'analisi del primo caso documentato nella Letteratura medica di sintomi riferibili a SAPM associata ad emicrania con aura evidenzia come tale entità possa comportare alcune difficoltà per un corretto inquadramento semeiologico e nosografico. Sebbene all'epoca questa condizione non fosse conosciuta, Charcot cercò di inquadrare il variegato complesso di sintomi riconducendoli all'emicrania con aura e all'epilessia. L'identificazione con l'epilessia sensitiva, sebbene discutibile, suggerì correttamente a Charcot che alcuni sintomi presentati dal paziente fossero riconducibili ad un disturbo dell'eccitabilità di aree corticali preposte all'elaborazione e alla percezione di stimoli sensitivi. Tale ipotesi fisiopatologica è attualmente supportata da studi neurofisiologici e di neuroimaging (1).

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## Spunti di riflessione sulla pandemia da COVID-19

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*Un libro “L’invasione della vita” (Mimesis, 2020) raccoglie valutazioni e riflessioni di studiosi appartenenti a varie aree, dall’etica alla psicoanalisi, dalla filosofia alla medicina, dall’ecologia alle scienze della comunicazione. Tra i temi affrontati: le relazioni con gli altri e tra le diverse generazioni, i problemi dell’ambiente e il mondo animale, i fenomeni della globalizzazione, l’etica della comunicazione, il ruolo della scienza e il difficile dialogo con la politica. Sul libro, la Società Filosofica Italiana (sezione del Verbano-Cusio-Ossola) ha organizzato mercoledì 24 febbraio un incontro telematico.*

*Pubblichiamo l’intervento di V. Grassi. È stato aggiunto un breve commento finale riguardante i capitoli che non erano stati oggetto di discussione durante l’incontro in quanto direttamente presentati dagli autori.*

Un interessante volume, che apre su un ampio raggio di argomentazioni, con diversi spunti di riflessione. Più immediata è la constatazione di come il libro sia stato scritto all’indomani della prima ondata della pandemia, in un contesto sociale ormai profondamente mutato; scritto oggi, il libro sarebbe diverso. Lo scorso anno vi erano certo vicende drammatiche e bilanci tragici, ma le drastiche restrizioni imposte furono condivise responsabilmente. Come scrive Giampiero Gamaleri: «Ora ci si vede attraverso uscite sui balconi per canti comuni e piccoli gesti di solidarietà reciproca».

Sarà stato forse l’utilizzo di un termine inglese allora sconosciuto, in luogo del più drastico italiano: “State in casa”; “State chiusi in casa”; fatto è che l’epidemia fu vissuta come una sfida che si poteva e si doveva vincere. Ricordiamo i suoni dalle finestre e dai balconi, i manifesti sull’eroismo dei sanitari o sull’ottimismo: “Ce la faremo”; “Andrà tutto bene”! Oggi di quel clima è rimasto ben poco; anzi, alla rabbia degli operatori economici e alle trasgressioni dei giovani si sono aggiunte forti tensioni sociali alimentate da campagne di odio ideologico diffuse dal web e che vanno

dal populismo, al negazionismo, al supremismo. Un quadro inquietante, che scompagina lo scenario composto e responsabile della scorsa estate.

Il libro evidenzia allora due problematiche contrapposte. La prima, ispirata al motto “Niente sarà più come prima”, auspica un profondo cambiamento, non solo del nostro modo di vivere: – economia, ecologia –, ma anche del nostro modo di essere: – il senso e il valore della vita, delle relazioni sociali –.

La seconda tendenza, che sembra oggi prevalere, vuole invece un ritorno acritico ad una “normalità” pre-pandemica. Come scrive Walter Minnella, a dar titolo al volume, l’epidemia è intesa come una “invasione della vita”, della nostra vita; di una vita, quindi, da recuperare integralmente: “La pandemia ci ha rubato qualcosa di ‘nostro’ che ci dev’essere restituito”.

Gli autori del volume prendono prevalentemente in considerazione la prima opzione, nelle varie implicazioni sociali e culturali. Si leggano gli auspici di Giampiero Gamaleri: «La sorprendente ripresa del senso religioso, così che resti almeno come capacità di comprensione, tolleranza, solidarietà e amore per i nostri simili»; o di Gian Piero Jacobelli: «Un nuovo stile di vita più consapevole e più responsabile. Un futuro che non può mai “cominciare” da solo, ma va sempre fatto “ricominciare” con l’impegno di tutti».

Nella stessa Presentazione si evidenziano «le criticità legate a scelte e strategie di sviluppo erronee od inique», per auspicare un ripensamento del nostro modo di relazionarci con gli altri e con il mondo, rispetto a quello che Minella chiama un «accecamiento dello sguardo verso il lontano»; «una distorsione della prospettiva». Vieni quindi ribadita una necessità di rifondare i valori della pace, della giustizia, della solidarietà; di gestire diversamente le sfide globali della finanza e dell’ambiente.

Ma la società sembra invece voler tornare al “come prima”, ovvero a una “normalità” che è vista come “nor-

ma” di comportamenti. In quest’ottica, ci saranno presto vaccini per gli USA e l’Europa; ma per il Terzo mondo, se e quando ci saranno. Manuela Monti e Carlo Alberto Redi citano un’emblematica scritta su una *villas* di Buenos Aires: «Non torneremo alla normalità, perché la normalità era il problema».

Ci fosse oggi un Leopardi a farci riflettere sulla nostra congenita fragilità, coniugata ad una sconfinata presunzione: «le magnifiche sorti e progressive»! Il *ben-essere* propagandato e rivendicato come condizione da ripristinare, perché per l’economia cambiare le cose non è “conveniente”.

Ne consegue che un mutamento di mentalità presuppone una riflessione sull’ontologia dell’essere: «Siamo stati obbligati a riflettere su problematiche importanti, quali le relazioni tra noi e gli altri. Ci siamo interrogati sul valore dell’esistenza».

A questo riguardo vorrei svolgere una breve riflessione su due citazioni riferite da Minella. La prima è del poeta John Donne, ripresa da Thomas Merton: «Nessun uomo è un’isola»; la seconda è di Margareth Teacher: «Non esiste qualcosa chiamato società. Esistono degli individui maschili e degli individui femminili che si uniscono per formare una famiglia».

Due tesi contrapposte, anche se il libro sembra orientato verso la prima, ovvero sul ruolo della società. *Nessun uomo è un’isola* significa che ogni uomo è una componente integrante dell’umanità, una parte di un tutto; come scrivono Monti e Redi: «La vita è per sua costituzione un’esperienza sociale».

La Natura ci genera come individui, e noi nasciamo certo attrezzati per diventare persone, ma solo la società finalizza il progetto. E questo rovescia l’assioma di Pirandello: è il rapporto con gli altri, con i centomila, che mi consente di acquisire un’identità.<sup>1</sup>

Fin dal grembo materno – come ricordava il compianto filosofo Pietro Prini – l’Io non esiste se non come rapporto viscerale con la madre. Un “Noi”; che si rafforza nei primi momenti di vita, quando i primi rapporti sociali sono quelli familiari.<sup>2</sup> Appartengono

ormai al linguaggio comune espressioni come “Recidere il cordone ombelicale”; “Complesso di Edipo”; “Uccidere il padre”, per evidenziare questo legame vitale.

Come sostiene Giuseppe Civitaresse: per «il superamento di una psicologia del soggetto visto come isolato» va ricordato che «alla nascita, per fare una mente ci vuole un’altra mente”. Se, con Rimbaud: “Io è un Altro”,<sup>3</sup> è allora possibile «vedere il soggetto come costituito da una gruppaltà interna composta dalla moltitudine delle identificazioni sedimentate nel corso della vita». In altre parole, a vent’anni io ero diverso da quando ne avevo quaranta e da quello che sono ora: io sono un divenire. Cosa mi ha reso diverso? Sono gli incontri, le relazioni, i rapporti.

Pier Giuseppe Milanese sottolinea che la scoperta dei neuroni specchio conferma questa evidenza: «Oggi il meccanismo dell’empatia viene più approfonditamente esplorato e studiato dopo la scoperta di popolazioni di neuroni che funzionano da specchio, su cui le azioni altrui si riflettono in noi stessi producendo le stesse reazioni. Il *logos*, quale principale organo della nostra specie, prima era presso Dio e poi si è fatto carne e abita in noi».

Ciò che ci caratterizza come persone è il pensiero, che è linguaggio, e il linguaggio nasce come risposta a un bisogno di comunicare, perché noi viviamo di relazioni; noi siamo strutturati come relazione.<sup>4</sup> Ma, se il linguaggio scientifico è diventato oggi l’orizzonte di senso, ne consegue che il mondo è una creazione della scienza.<sup>5</sup>

Concludo con una distinzione tra la solitudine, che può essere una libera scelta: “*Beata solitudo; sola beatitudo*”, e l’isolamento, che equivale a una restrizione, privazione: ci manca qualcosa, ci manca l’altro; e questo sia nel bene che nel male. Abbiamo visto che l’essere costretti in casa rafforza i legami positivi e de-

1 - L. PIRANDELLO, *Uno, nessuno e centomila*, Firenze, R. Bemporad, 1926.

2 - P. PRINI, *Lo scisma sommerso*, Interlinea, Novara 2016, p. 109: «L’antropologia contemporanea è giunta a un chiarimento essenziale, quando ha scoperto che l’uomo è sociale fin dal principio. Il Noi precede l’Io, o più precisamente lo costituisce come relazione originariamente reciproca tra gli Io».

3 - A. RIMBAUD, lettera del 13 maggio 1871 al prof. Georges Izambard: «È falso dire “Io penso”; si dovrebbe dire “Mi si pensa”. Scusi il gioco di parole: IO è un altro».

4 - P. PRINI, *Discorso e situazione*, Studium, Roma 1975, p. 44: «Siamo condizionati, modellati e predisposti dal linguaggio, in tutti i nostri comportamenti mentali».

5 - U. GALIMBERTI: «Il linguaggio parla, e con il nome determina il modo di presentarsi della cosa e quindi ogni suo possibile senso»; «In un mondo dominato dalla tecnica, in cui la stessa domanda sui fini sembra insensata, ciò che si richiede ai singoli esseri umani non è una particolare creatività, o capacità d’empatia nei confronti del prossimo, ma la “professionalità”, per usare un termine orribile, oggi divenuto sinonimo di virtù»; [http://www.fisicaedintorni.it/dtml/uomo\\_e\\_tecnica](http://www.fisicaedintorni.it/dtml/uomo_e_tecnica)

genera quelli negativi: rancori, litigi, violenze domestiche, femminicidi. Un personaggio di Sartre diceva: «L'inferno sono gli altri!». Ma «*l'inferno sono gli altri*» intende constatare l'impossibilità di un'esistenza che escluda l'Altro, perché dall'alterità non si può uscire; perché ci si rende conto che l'Altro detiene il segreto del nostro essere».<sup>6</sup>

Se nella solitudine io sono in me, nelle relazioni io sono nello sguardo degli altri, pena la perdita di senso. Leopardi aveva anticipato questa deriva, nell'amara descrizione della vecchiaia: «Quando muti questi occhi all'altrui core, e lor sia voto il mondo».

L'isolamento equivale all'emarginazione: l'essere messi da parte, esclusi. E oggi, viziati da un rapporto sociale basato sul profitto, il non contare più equivale a un non essere più: «Che cosa devo fare della vita? Che cosa mi può dare la vita?». La vita, ridotta a una relazione utilitaristica tra ciò che io do e quello che la vita mi dà, si configura così come un rapporto tra produttore e consumatore.<sup>7</sup>

Viene in tal modo scardinato il valore del tempo, soprattutto quello da dedicare a noi stessi; come l'*otium* dei latini, ovvero lo spazio della cultura, della riflessione, dei rapporti affettivi. L'unica alternativa è un *disvertere*, ovvero il divertimento del «buon-tempo[ne]».

Il marchio dell'*homo faber*, produce inevitabilmente degli scarti, ovvero gli emarginati che non sono funzionali al sistema. Nel conteggio dei decessi pandemici serpeggiava una sorta di assuefazione: «Sì; ma sono anziani!». Basata sull'attivismo e sull'efficienza, la società finisce per emarginare di fatto quanti non rientrano in quest'ottica; in tal modo, è alla fine del percorso, negli ospizi dei vecchi, che l'Uno diventa Nessuno!

La televisione ci mostra centenari autosufficienti, lucidi, attivi; ma chi ha fatto esperienza delle case di riposo ha negli occhi la pena di tanti sguardi assenti, spenti; quelle lunghe interminabili ore nella vana atte-

sa di qualcosa o di qualcuno; le amare, sconsolate considerazioni: «Cosa vivo a fare? Non faccio niente; non servo a niente!».

Adelaide Baldo parla dei vecchi come «Corpi senza progetto, senza parola, senza identità. Le RSA sono luoghi tristissimi dove si va per morire. Una meta che destina molti a un limbo afono e solitario, prima di raggiungere la meta verso cui tutti andiamo».

E così, questa diffusa persuasione derubrica ormai come insignificante la prospettiva

escatologica di un aldilà come «riposo eterno»: un vuoto e disperato «far niente».<sup>8</sup>

Accanto a queste problematiche filosofico-esistenziali il libro affronta alcuni altri aspetti ad esse più indirettamente legati. La pandemia è frutto di una politica di devastazione ambientale che è stata la causa principale dei fenomeni di «spillover» (ovvero di salto di specie del virus dall'animale all'uomo) che vengono analizzati da uno storico della medicina, Paolo Mazzarello, che evidenzia anche gli aspetti inediti di questa pandemia rispetto a quelle del passato. Gli aspetti etici sono centrali nel capitolo di Giannino Piana che sottolinea come senza una svolta radicale, senza un nuovo modello di civiltà il mondo sia destinato a convivere sempre più frequentemente con eventi catastrofici. E' anche il rapporto tra scienza e società, come sottolinea Giorgio Sandrini, che è andato in crisi o per lo meno ha evidenziato gravi e preoccupanti limiti. Se la scienza ha contribuito a contenere il pur elevatissimo numero di vittime, il suo uso non etico alla base di molti dei fenomeni che caratterizzano la cosiddetta «globalizzazione» è stato direttamente od indirettamente responsabile della diffusione della pandemia con una rapidità e dimensione mai precedentemente osservate. Il rapporto conflittuale tra scienza e società e l'uso inappropriato della prima da parte della seconda, ci obbligano ad una profonda e non più rinviabile riflessione.

6 - J.P. SARTRE, *Porta chiusa*, trad. di G. Lanza e M. Bontempelli, Bompiani, Milano 2013. EMILIA BEZZO, [arenaphilosophika.it/author/emilia-bezzo/](http://arenaphilosophika.it/author/emilia-bezzo/).

7 - P. PRINI: «L'uomo borghese dell'età della scienza e della tecnica si risolve nel suo proprio lavoro e nelle sue opere: vale per quello che a fare», *Discorso e situazione*, Studium, Roma 1961, p. 66.

8 - «Oggi la tecnica erode le fondamenta del trono di Dio, proprio riducendo la nostra esperienza del tempo: se tutto si risolve nella scelta dei mezzi più idonei in vista di un fine immediato, se le nostre aspettative si estendono su un arco di poche ore o giorni, questo presente assoluto sostituisce l'attesa dell'*éschaton*, di un compimento definitivo della storia»; U. GALIMBERTI, *cit.*

## Silver economy una oportunidad de desarrollo

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**Resumen.** Vivimos en una sociedad envejecida en la que existe una gran demanda de servicios sociales, de asistencia sanitarias y atención a personas mayores. Estos servicios, necesarios y obligados en pro del bienestar de los mayores, junto con la extinción de la vida laboral, provoca un impacto notable en diversos sectores de la sociedad, como la economía, incluyendo el mercado laboral, los mercados financieros, el los bienes y servicios necesarios para los mayores adultos (vivienda, transporte, ocio), la sanidad y la política. Ante esta situación, surgió hace algo más de una década, el concepto de economía plateada, como opción de cambio social y económico, para adecuar el envejecimiento demográfico a la esperanza de vida actual, de forma que se estableciese una estrategia económica sostenible, aprovechando el potencial profesional de las personas mayores. Este artículo pretende analizar la producción científica realizada en este campo, mediante una revisión bibliográfica de artículos a través de la consulta en veinte bases de datos, con el objeto de conocer, las potencialidades de la Silver Economy en distintas regiones del mundo, así como las barreras acaecidas en su implantación, las políticas y estrategias llevadas a cabo para su desarrollo.

**Palabras clave:** silver economy, economía plateada, política, gerontecnología, ética.

### SILVER ECONOMY A DEVELOPMENT OPPORTUNITY”

**Summary.** Today we live in a highly aged society in which there is a great demand for social services, health care and care for the elderly. These services, necessary and required for the welfare of the elderly, together with the extinction of working life, causes a notable impact on various sectors of society, such as the economy, including the labor market, financial markets, goods and services necessary for older adults (housing, transport, leisure), health and politics. Faced with this situation, the concept of a silver economy emerged a little more than a decade ago, as an option for social and economic change, to adapt demographic aging to current life expectancy, so that a sustainable economic strategy was established, taking advantage of the career potential of older people. This article aims to analyze the scientific production carried out in this field, by means of a bibliographic review of articles through the consultation in twenty databases, in order to know, the potentialities of the Silver Economy in different regions of the world, as well as the barriers encountered in its implementation, the policies and strategies carried out for its development.

**Keywords:** silver economy, silver economy, politics, gerontechnology, ethics.

### SILVER ECONOMY UN’OPPORTUNITÀ DI SVILUPPO

**Riassunto.** Viviamo in una società che invecchia in cui c’è una grande domanda di servizi sociali, assistenza sanitaria e assistenza agli anziani. Questi servizi, necessari per il benessere degli anziani, insieme alla forte riduzione della vita lavorativa, provocano un notevole impatto su vari settori della società, come l’economia,

compreso el mercado del trabajo, i mercati finanziari, i beni e i servizi necessari per gli anziani adulti (alloggio, trasporti, tempo libero), salute e politica. Di fronte a questa situazione, il concetto di “silver economy” è emerso poco più di un decennio fa, come opzione per il cambiamento sociale ed economico, per adattare l’invecchiamento demografico all’attuale aspettativa di vita, in modo da stabilire una strategia economica sostenibile, sfruttando la carriera potenziale delle persone anziane. Questo articolo si propone di analizzare la produzione scientifica svolta in questo campo, attraverso una rassegna bibliografica degli articoli attraverso la consultazione in venti banche dati, al fine di conoscere le potenzialità della Silver Economy in diverse regioni del mondo, nonché gli ostacoli incontrati nella sua attuazione, le politiche e le strategie messe in atto per il suo sviluppo.

**Parole chiave:** silver economy, politica, gerontecnologia, etica

## Métodología

El método utilizado fue una investigación de todos los artículos publicados en lengua castellana e inglesa, a partir del descriptor *Silver Economy* en las bases de datos de: “SciELO”, “UAM”, “PePSIC”, “LILACS”, “PubMed”, “APAPsycmet”, “PsyncINFO”, “Dialnet”, “Teseo”, “UOC”, “Medine”, “CINAHL”, “Psychology and Behavioral”, “COCHRANE”, “Scopus”, “Google-Academics”, “La Referencia”, “Microsoft Academic”, “RedIb”, “World Wide Science”.

Los artículos encontrados inicialmente fueron 6.774. Todos ellos se sometieron a un proceso de revisión, dando por válidos aquellos artículos accesibles libremente en cada una de las bases de datos, resultando ser válidos el número de artículos de 1.973. Posteriormente, se realizó un segundo análisis y corte basado en la lectura del título y el resumen de cada uno de ellos. Cuando esto no fue suficiente para decidir la inclusión o exclusión del artículo, porque el título no representaba el núcleo del artículo o el resumen era muy sucinto y dejaba dudas sobre la relevancia de la inclusión, también se analizaron muestras, de resultados y conclusiones de dichos artículos. Para la exclusión: también se utilizaron los criterios: artículos no disponibles en su totalidad de forma gratuita, duplicados y/o sin criterios de revisión. De ellos, 32 artículos fueron excluidos por estar duplicados en distintas bases de datos. Los artículos seleccionados y considerados potencialmente relevantes (N=275) fueron revisados a partir del análisis del título/resumen y del análisis de la muestra y resultados. Los criterios de inclusión fueron: estudio

sobre el tema propuesto (investigación sobre *Silver Economy*, o economía plateada). Tras este análisis fueron excluidos 183 artículos. Finalmente, los artículos relevantes revisados fueron 60. El Anexo I contiene el diagrama de flujo elaborado donde se condensa el proceso de búsqueda y selección del material a analizar, mostrándolo de forma sintética y permitiendo una visión global del mismo. El análisis de los resultados ofreció diferentes cuestiones discutidas.

## Resultados y analisis de datos

La revisión bibliográfica realizada ha puesto de manifiesto el incremento de investigaciones y análisis relacionados con la evolución de la esperanza de vida y la evolución demográfica, y su vinculación con la economía plateada. De hecho, los últimos 5 años han sido los más fértiles en este tema, albergando algo más del 80% de las producciones (figure 1).

Las metodologías utilizadas en los artículos revisados son diversas (Figure 2), siendo la metodología más utilizada la del *Análisis Descriptivo*, el cual fue seguida en el 50% de los artículos revisados. El segundo método fue la *Revisión Bibliográfica*, seguida de la *Investigación Cualitativa Exploratoria* bajo una *Guía de Entrevista semi-estructurada*. También se utilizó en algunos de ellos el *Metanálisis* y *Análisis Estadísticos*, y el *Análisis Comparativo Cualitativo (QCA)*, como métodos más usuales.

Esta amplia producción literaria nos ha permitido analizar, en términos generales, el cambio demográ-

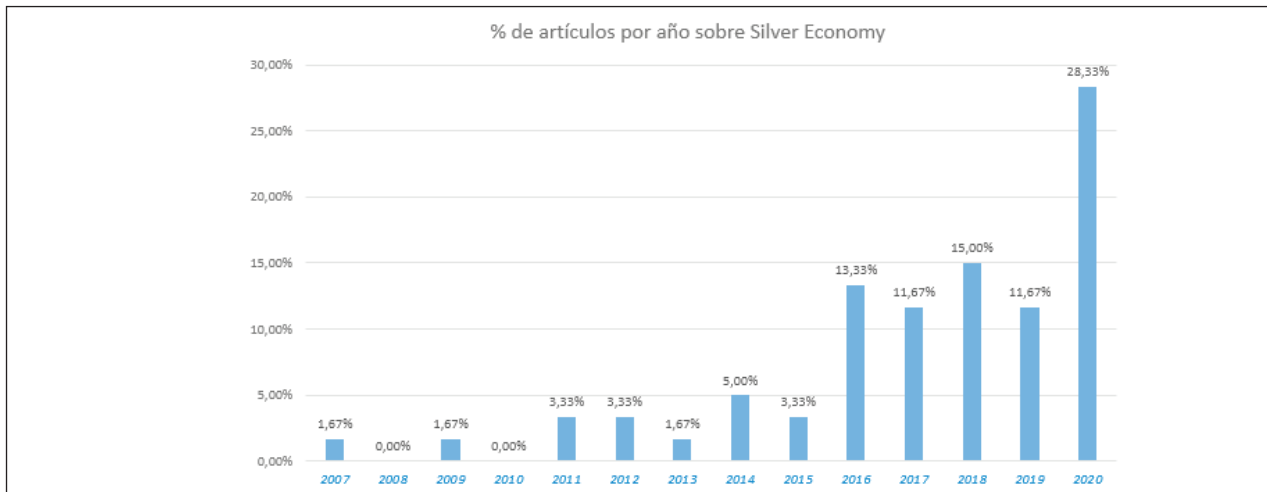


Figure 1.- % de artículos revisados sobre la Silver Economy en las últimas dos décadas. Fuente: elaboración propia

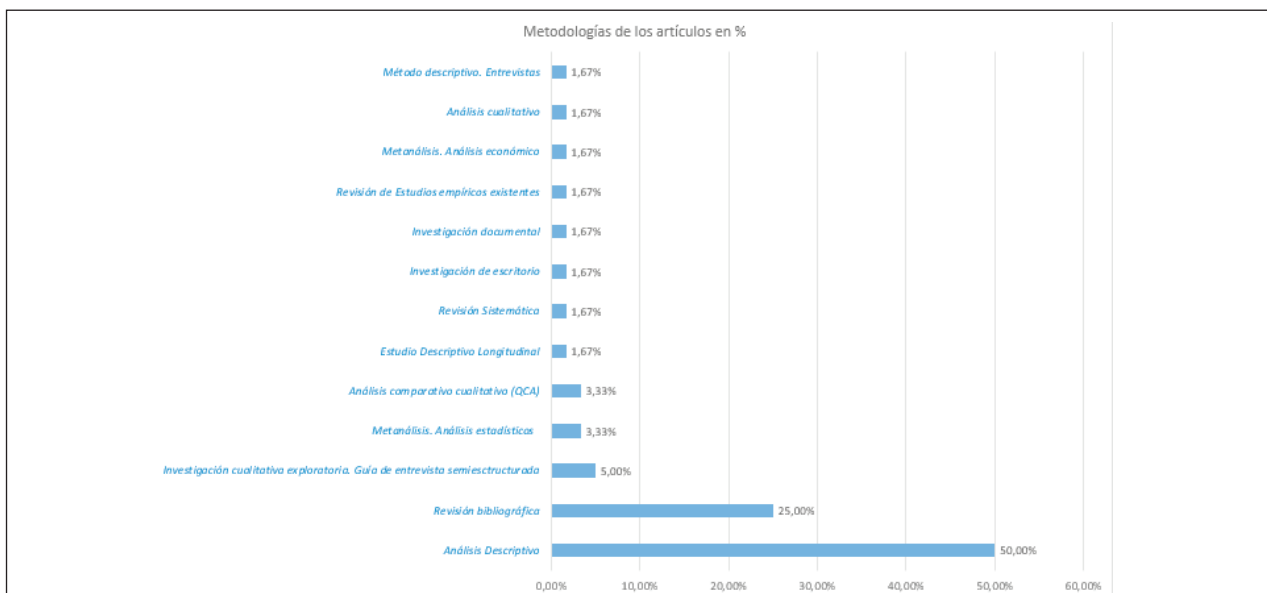


Figure 2. Metodologías utilizadas en los artículos revisados. Fuente: elaboración propia

fico que acompaña a la sociedad de hoy en día, una población cada vez más envejecida, donde la proporción de personas mayores aumenta año tras año, lo que conlleva un aumento en los servicios de atención a las personas mayores y otras muchas exigencias sociales. A su vez, dado que el envejecimiento también se asocia con una disminución de la tasa de fecundidad, florecen otras preocupaciones, referidas a una reducción en la entrada de recursos laborales jóvenes en el mercado laboral y, por otro lado, un aumento de la carga de

mantener la generación anterior y satisfacer sus necesidades específicas y costosas, de forma que el problema del envejecimiento suscita, en la Unión Europea, un impacto significativo en el conjunto de la sociedad en términos económicos. Así, en la bibliografía revisada, el problema del envejecimiento poblacional es contemplado desde distintas ópticas (figure 3), donde el 35% de los artículos lo vinculan con problemas futuros en servicios asistenciales, el 8,33% de ellos, lo relacionan con problemas en las esferas económicas, sociales y po-



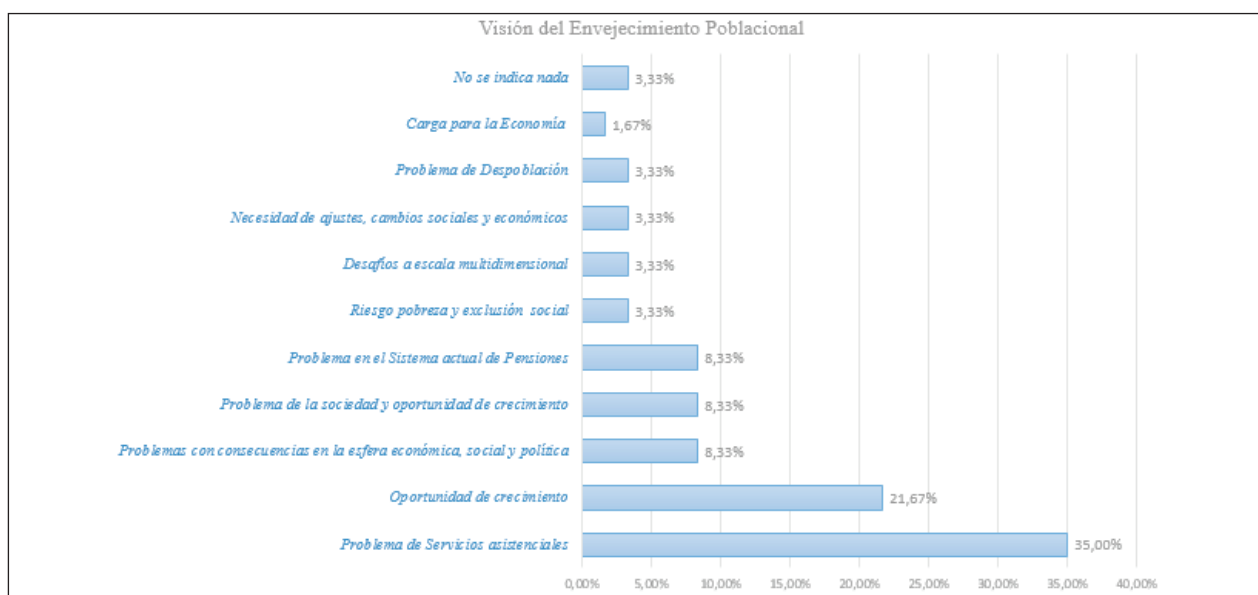


Figure 3.- Visión del Envejecimiento poblacional en los artículos revisados. Fuente: elaboración propia

líticas, otro 8,33% de los artículos lo consideran como un posible problema en el sistema actual de pensiones. En un 3,33% de los artículos se pone de manifiesto que este envejecimiento poblacional vendrá asociado con desafíos a escala multidimensional, o con riesgos de pobreza y exclusión social de las personas mayores. Por el contrario, el 21,67% de los artículos ofrece una visión optimista del envejecimiento de la población, al contemplarlo como una oportunidad de crecimiento económico e integrador de las personas mayores. Al igual que un 8,33% de los artículos, que ven el envejecimiento de la población como un problema que aparece en la sociedad que puede a su vez ser una oportunidad de crecimiento y desarrollo económico.

Para resolver estos problemas derivados del envejecimiento poblacional en la sociedad actual, han de articularse soluciones factibles, vinculadas con la realidad, y vehiculizadas a través de una herramienta tanto social, como política. En cualquier caso y también es algo más que evidente, un solo indicador no es suficiente para determinar un modelo de crecimiento o un modelo de sociedad. De la misma forma que el PIB no lo es todo, tampoco lo es el envejecimiento y la sociedad debe decidir y elegir su modelo de desarrollo que seguro debe implicar, más digitalización, más emprendimiento, más energía fotovoltaica en los tejados, más energía barata para las personas mayores, más salud y

dedicación a las personas mayores, etc.. Y sobre todo que genere empleo y dedicación satisfactoria a favor de y por la población adulta.

En este sentido unas directrices políticas en materia económica, social, de infraestructuras, etc...bien dirigidas, serían las mejores herramientas para proponer soluciones.

Si observamos la gráfica anterior (figure 4), el 10% de los artículos recogen referencias a políticas de apoyo a la economía plateada, un 8,33% de los artículos hace mención a políticas públicas, mientras que otro 8,33% alude a políticas de envejecimiento activo y saludable, como opciones necesarias para llevar a efecto la economía plateada en sus sociedades. De igual modo, otros artículos establecen la necesidad de impulsar políticas orientadas al mercado laboral, a la seguridad social, al sistema de salud y a la educación (6,67%), y un 5% de los artículos considera vital el establecer una política de cambios en la sociedad, para impulsar soluciones al envejecimiento poblacional.

Estas soluciones que se puedan plantear desde las distintas políticas, encauzan en un denominador común, la *Silver Economy* (economía plateada), es decir, la economía basada en los bienes y servicios orientados a las personas mayores de 55 años.

Así, los artículos revisados, contemplan el concepto de economía plateada vinculado con nociones y

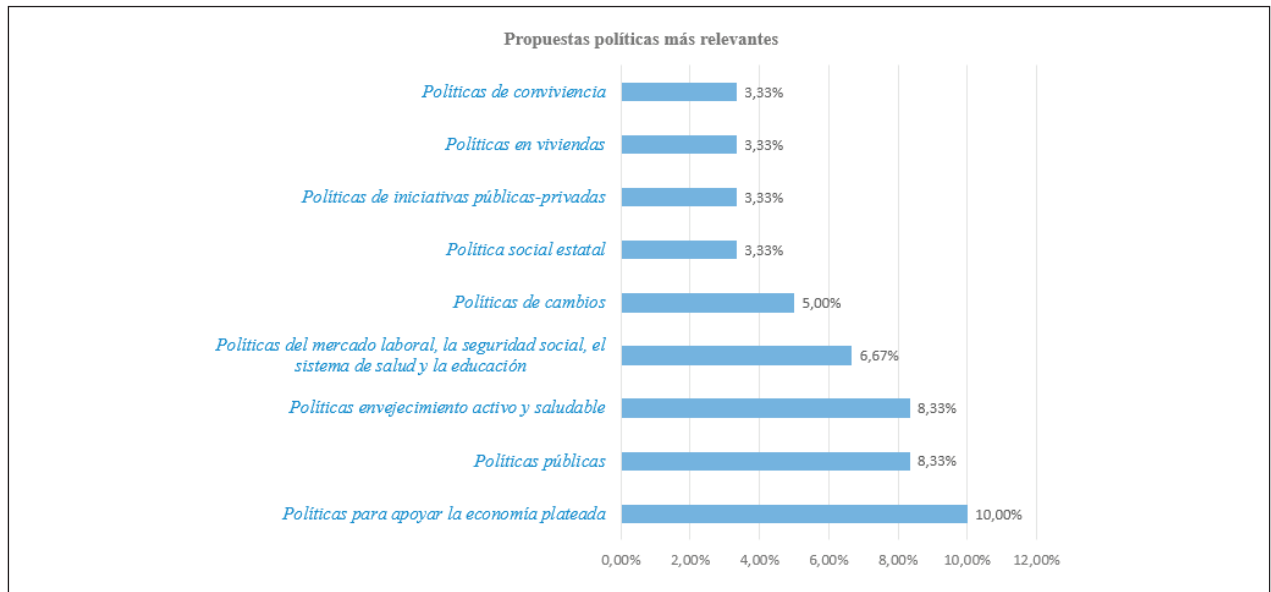


Figure 4.- Políticas más relevantes recogidas en los artículos revisados. Fuente: elaboración propia

aspectos económicos paralelos, nuevos, u opcionales, de forma que, el 36.67% de los artículos contemplan la economía plateada como una oportunidad de cre-

cimiento económico. De hecho, desde un punto de vista macroeconómico, el desarrollo de la economía plateada, y según las previsiones de los principales or-

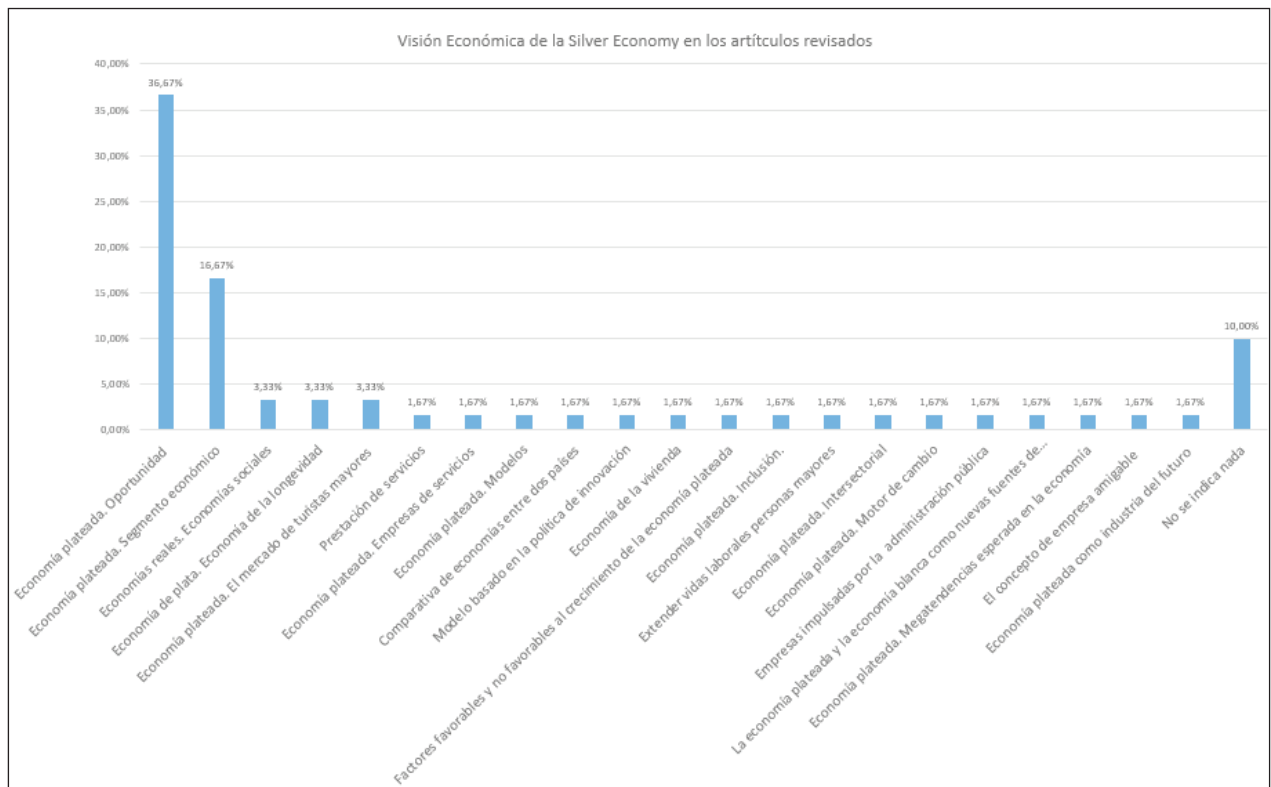


Figure 5.- Visión económica de los artículos sobre la Silver Economy. Fuente: elaboración propia.

ganismos internacionales y centros de investigación, será, en los próximos años, una de las megatendencias esperadas en la economía (6). Es por ello, que también muchos de los artículos (16,67%), consideran la economía plateada como un nuevo segmento económico. Este pensamiento tal vez está regido por la idea de que la economía plateada es un nuevo mercado, un mercado de consumo de productos y servicios diseñados para la población de adultos mayores y que surge de la necesidad de aumentar la sostenibilidad del gasto público vinculado al envejecimiento (Comisión Europea, 2015).

Pero además de verse como un nuevo segmento económico, un segmento lleno de oportunidades de generación de riquezas. La economía plateada es vista en los diferentes artículos, con otras acepciones positivas y deseables, en contraposición a la óptica con la que se apreciaba años atrás al mercado de los adultos mayores, como un mercado indeseable. En este sentido, esta visión está cambiando paulatinamente debido al cambio demográfico, y dado que los adultos mayores se están volviendo importantes para muchas empresas como clientes potenciales que son financieramente independientes (16).

Así, en los artículos se recogen referencias de la economía plateada vinculados con términos como: Economías reales. Economías sociales (3,33%), Economía de plata. Economía de la longevidad (3,33%), Economía plateada. El mercado de turistas mayores (3,33%), Prestación de servicios (1.67%), Economía plateada. Empresas de servicios (1.67%), Economía plateada. Inclusión. (1.67%), Economía plateada. Intersectorial (1.67%), Economía plateada. Motor de cambio (1.67%), La economía plateada y la economía blanca como nuevas fuentes de crecimiento (1.67%), Economía plateada. Megatendencias esperada en la economía (1.67%), El concepto de empresa amigable; Economía plateada como industria del futuro (1.67%).

Hay que puntualizar que, durante las últimas décadas, las empresas se centraron en los grupos de consumidores más jóvenes porque los adultos mayores eran, según los estereotipos, individuos económicamente débiles y consumidores muy reticentes (Meiers, 2014) pero hoy deberán estar más preparados para aceptar requisitos especiales de los adultos mayores. a medida que la población envejece (Moschis y Pettigrew, 2011).

En definitiva, la economía plateada es un serio estímulo para el desarrollo, siempre que se base en supuestos axiológicos de desarrollo social de acuerdo con el enfoque de desarrollo centrado en las personas, asignando subjetividad al individuo y al grupo en la mayor medida posible. El desarrollo de la economía plateada es posible sobre la base de reglas éticas que promueven la inclusión social y económica y contrarrestan las consecuencias negativas de los estereotipos, la discriminación por edad y la exclusión social.

En este sentido, en muchos de los artículos revisados se recoge la percepción de la sociedad sobre las personas mayores adultas de 55 años, y las barreras que se establecen en la economía plateada por los prejuicios negativos que aún se tienen en muchas de las sociedades del mundo.

De hecho, la esencia del problema está en la implementación de la economía plateada, y la relación que existe con el rechazo de sesgos y estereotipos sobre las personas mayores. El análisis del problema nos lleva siempre a las acciones e intervención de la vejez en la sociedad y la aceptación de nuevos roles. Y es que, en el contexto público, domina una visión negativa de la dinámica demográfica, centrado, a veces, en el discurso repetitivo de aumento del gasto de la seguridad social (salud, sistemas de pensiones y asistencia social). Así, en algunos de los artículos se recogen (figure 6) los estereotipos más frecuentes: se habla con una connotación negativa del término vejez, la prevalencia del temor a la mala calidad del trabajo de las personas de más de 50 años, los prejuicios sobre la resistencia de las personas mayores a aprender y aceptar lo nuevo, el contemplar a las personas mayores como grupo objetivo poco atractivo, demasiado exigente, pero que no genera beneficios potenciales sustanciales para las empresas. A veces, lo contemplan como una amenaza, o un lastre para las perspectivas de futuro de la economía y la sociedad. Otras veces, lo califican como factores de mercado no significativos.

Estos dilemas éticos subrayan la necesidad de reflexionar sobre el problema, y plantear soluciones efectivas, que, aunque no obtengan resultados inmediatos, si generen un cambio de mentalidad de la sociedad hacia los mayores. Hay que intentar limitar el impacto negativo de estos prejuicios, empezando por definir nuevos ideales sobre las personas mayores. Las personas mayo-

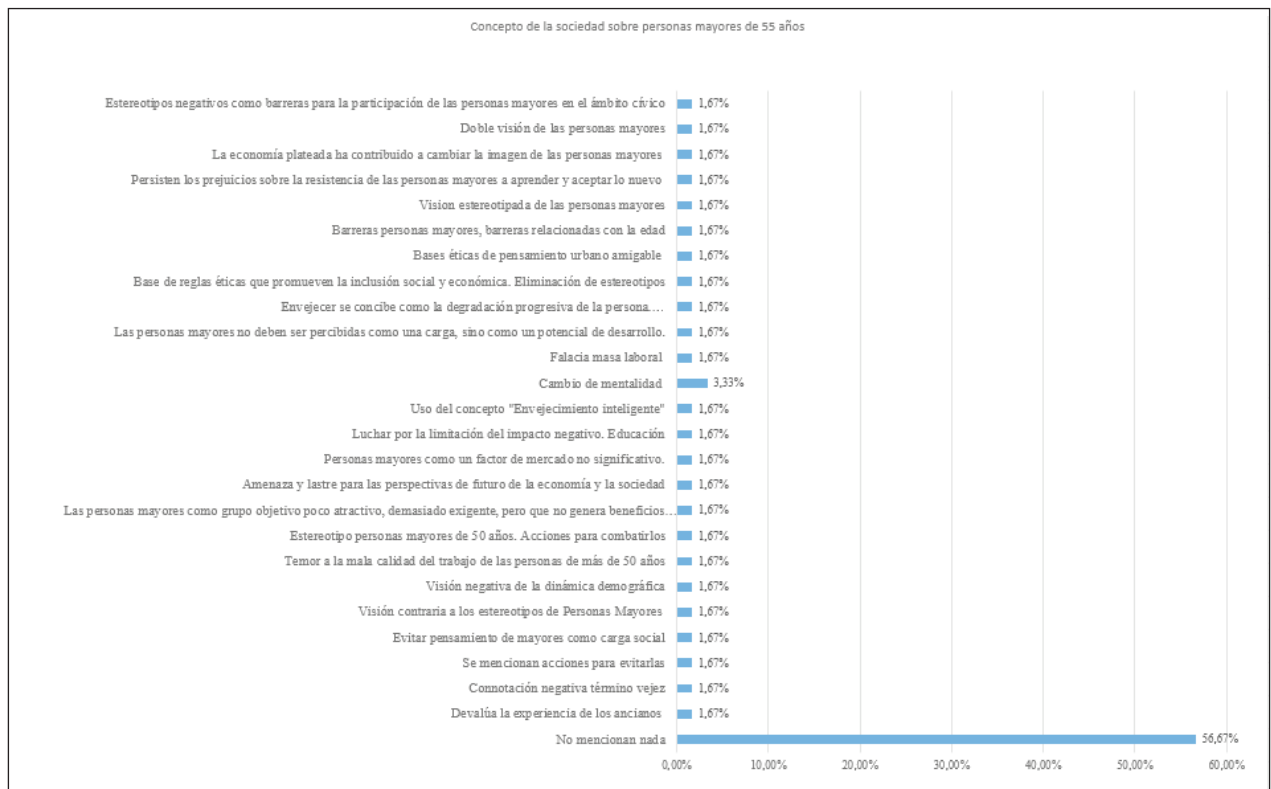


Figure 6.- Concepto de la sociedad sobre personas mayores adultas. Fuente: elaboración propia.

res no deben ser percibidas como una carga, sino como un potencial de desarrollo. Para ello, podría ser interesante el utilizar conceptos como "Envejecimiento inteligente", y hacer partícipe a las personas mayores en distintos estamentos de la sociedad. La economía plateada puede contribuir a cambiar la imagen de las personas mayores, ya que las contempla como un valioso capital humano, que también puede contribuir al desarrollo social y económico de su entorno.

Los avances tecnológicos que han tenido lugar en últimas décadas han permitido, no solo, un incremento de la esperanza de vida, sino también una mejora del envejecimiento. Además de los diversos factores que afectan decisivamente a la longevidad, como la alimentación, la actividad física, el ambiente socio-cultural, el descanso, el ambiente socio-cultural, han sido los avances tecnológicos en campos tan fundamentales como la informática, la medicina, la salud, las políticas sociales las que han permitido incrementar los años de vida permitiendo vivir con buena hasta algo más de los setenta años.

Según la Organización Mundial de la Salud (2002: 12), el envejecimiento activo puede definirse como "el proceso de optimización de oportunidades de salud, participación y seguridad con el fin de mejorar la calidad de vida como las personas envejecen".

El envejecimiento de la población se caracteriza por un aumento de la duración de la vida humana, lo que favorece el desarrollo de bienes y servicios para los consumidores mayores y las sociedades que envejecen. El creciente interés en este contexto ha llevado al concepto de la "economía plateada".

Este aumento de la esperanza de vida conlleva un impacto directo sobre distintos sectores de la sociedad como la economía, el sistema sanitario incluido el cuidado de las personas mayores, la política y la sociedad en general. La revisión bibliográfica ha puesto de manifiesto muchos de estos dilemas, desde distintas ópticas, acompañadas de propuestas para atenuar en incluso revertir dichas disyuntivas.

## Conclusiones

La discusión realizada en el apartado anterior, sobre las ideas más relevantes de los artículos revisados, vislumbra, de forma fehaciente, que la economía plateada es un área de potencial crecimiento, del cual se espera que un gran número de sectores económicos se beneficien de ella, sectores tan diversos como la cosmética y la moda, hogares inteligentes, TIC, servicios de salud (incluidos dispositivos médicos, productos farmacéuticos y eSalud), fitness y bienestar, servicios de robótica, finanzas y seguros, seguridad, cultura, educación y habilidades, entretenimiento, transporte y, por supuesto, turismo (33).

Y es que, los adultos mayores tienen necesidades crecientes de la seguridad de sus medios ambientes y sus hogares y requieren productos y servicios adecuados a sus capacidades funcionales (30).

Para ello, la gerontecnología podría ayudar a proponer soluciones al envejecimiento demográfico. La tecnología Geron está relacionada con el diseño de medios electrónicos de la vida cotidiana, como soluciones para trabajo remoto, sensores, alarmas, dispositivos para mejorar la audición, el olfato y la visión, sistemas de baño, así como hogares inteligentes. Sin duda, el campo de la salud es el más afectado por los procesos tecnológicos, y algunas de las áreas de tecnologías innovadoras de más rápido desarrollo son la telemedicina y la teleóptica.

Según Gschwendtner, P. (11) la tecnología y la innovación ofrecen soluciones potenciales a los desafíos creados por la transformación demográfica hacia las poblaciones mayores. Esto demuestra que los gobiernos pueden influir y orientar la actividad de I + D / CTI con medidas adecuadas para ayudar a convertir los desafíos en una oportunidad económica y social.

Es necesario tener en cuenta este arquetipo en la configuración de las políticas innovadoras, y las tareas de las entidades incluidas en la transferencia de tecnología y comercialización de sistemas de conocimiento. De esta manera, el apoyo a la gerontecnología también puede ser considerado como un importante instrumento de desarrollo regional, si se conforman estructuras permanentes de cooperación de organismos que representen a la administración pública, empresas y organizaciones no gubernamentales (apoyo empresa-

rial e instituciones de economía social) (17).

Por tanto, las políticas públicas podrían orientarse a acciones de cohabitación de la tecnología con las personas mayores, y fomentar cuatro acciones fundamentales, tal y como detalla Klimczuk, A. (17), el cual propone: 1.- Mayor promoción del conocimiento sobre los conceptos de economía plateada y *gerontecnología*, tomando en cuenta la diversidad interna de las personas mayores; 2.- Evitar la discriminación por edad en el diseño y promoción de modelos de *gerontecnología* y economía plateada; 3.- Conformar instituciones científicas y educativas especializadas en *gerontecnología* como "*AgeLab*" y ubicar los planes de estudio de esta disciplina en las universidades; 4.- Popularización de instituciones culturales como "*MediaLabs*" - interdisciplinar, abierto a la actividad pública, coadministrado, construyendo vínculos entre negocios, ciencia y social.

Así mismo, este desarrollo tecnológico podría orientarse a ofrecer soluciones en el entorno de la sociedad en la que se desenvuelven las personas mayores, es decir, entornos urbanos, incluidas las viviendas, con el objeto de hacerlos más seguros y fiables. Hay que recordar que, las dolencias de salud más costosas en las personas mayores son las caídas, que a menudo causan lesiones graves. Y es que la accesibilidad a un entorno amigable con las personas mayores que pueda acomodar las capacidades funcionales de los residentes y el desarrollo de viviendas con cuidado son dos factores importantes que pueden permitir que los adultos mayores vivan más tiempo en sus comunidades. La creación de entornos urbanos adaptados a las personas mayores es, por tanto, una de las inversiones más eficaces que se pueden realizar como respuesta al cambio demográfico. Los adultos mayores, como el grupo demográfico de más rápido crecimiento en Europa, influirán en la estructura de la demanda de productos y servicios y, por tanto, aumentará la proporción de procesos de producción y servicios para los adultos mayores (30).

En lo que respecta a uno de los nefastos impactos del cambio demográfico, la despoblación de zonas rurales, la implantación de la economía plateada, enfocada a personas mayores, podría ser una alternativa para tratar de paliar dicha situación. Ejemplos como los de la región de Lubusz, podrían ser una opción real para diversas regiones de la Europa actual. Para ello, se debería de potenciar aquellos aspectos que más interesan

a los mayores, dentro del marco de la economía plateada. Como referencia, B. Cupial y E. Sobolewska-Poniedzialek (5) argumentan, tras el análisis de dicha provincia, las fortalezas de la región, que podrían ser promovidas por provincias con entornos similares. Entre las fortalezas de Lubusz se encuentran: una ubicación conveniente en las principales rutas de transporte nacionales, una red bien desarrollada de empresas existentes en el sector de la pequeña y mediana empresa, una riqueza natural y cierta diversidad de atracciones turísticas, así como numerosas instituciones de atención para personas mayores existentes.

Es, por tanto, decisivo establecer políticas alineadas con el envejecimiento activo, que hagan participe a las personas mayores en la sociedad, de una forma activa e integradora, incluyendo intervenciones públicas concretas, para mantener la solidaridad entre generaciones y prevenir la exclusión de los trabajadores.

Así, en la literatura revisada, se establecen diversas sugerencias sobre el desarrollo de políticas económicas y políticas del Estado en relación a estas intervenciones. Por ejemplo, en el artículo de Kolomiets, P. N. (20), se recogen algunas de las políticas establecidas en Rusia que se podrían llevar a cabo para impulsar la Economía Plateada (Silver Economy), estimulando la vitalidad y el desarrollo del empleo en la actual sociedad que envejece. Algunas áreas a destacar de dicha política implican a los sectores siguientes: Sector Económico; Sector de Cuidado de las Personas Mayores; Sector Político; Sector Sociedad; Gerontotecnología.

Como consecuencia de todo ello las principales conclusiones y aportaciones alcanzadas en el análisis de las temáticas revisadas son las siguientes:

- 1) **Productos para la tercera edad:** Desarrollo de la producción de productos para la tercera edad, otorgando beneficios a los fabricantes de productos para el cuidado de la tercera edad. Promover la investigación de los mercados de servicios para las personas mayores e identificar los productos faltantes necesarios.
- 2) **Aprovechamiento las oportunidades:** Las personas mayores ciertamente aprovecharán las oportunidades para extender su longevidad laboral, especialmente si su iniciativa es realmente apoyada por los programas federales ya declarados: un programa que regula las opciones de jubilación; un programa

de adaptación de los lugares de trabajo a las peculiaridades de la mentalidad y el bienestar físico de los trabajadores mayores; programa de educación continua; programa social para reducir el nivel de discriminación por edad.

- 3) **Adaptación y accesibilidad:** Debería prestarse la debida atención a la adaptación y accesibilidad de las instalaciones para personas con discapacidad. Las empresas constructoras y las autoridades municipales deben desarrollar y adoptar normas para un “medio ambiente universal” y adoptarlas debidamente en el futuro diseño de edificios y planificación urbana.
- 4) **Información y colaboración:** Informar a la sociedad sobre los problemas de las personas mayores. Creación de condiciones favorables para la creación de sociedades no estatales de apoyo a las personas mayores. Creación de condiciones favorables para la organización de debates, conferencias y debates sobre envejecimiento. Facilitar la cooperación de especialistas que se ocupan de los problemas del envejecimiento en diferentes niveles e industrias. Encuentre un mecanismo de colaboración entre comunidades / organizaciones e instituciones de servicios relevantes.
- 5) **Apoyo social:** Se necesita un sistema de apoyo social para las personas mayores. El gobierno ruso debería acumular gradualmente reservas financieras para pagar los servicios de cuidado de personas mayores. Asimismo, las autoridades competentes deben prever el número óptimo de profesionales asistenciales (trabajadores sociales, enfermeras, fisioterapeutas, terapeutas ocupacionales, gerontólogos) e iniciar su formación. Se requiere que los especialistas estén capacitados en las últimas técnicas y protocolos de acuerdo con el desarrollo e implementación de las últimas tecnologías, así como que desarrollen mecanismos de recertificación y reciclaje.
- 6) **Control de la salud:** Para abordar con éxito los problemas relacionados con el envejecimiento, las autoridades sanitarias locales deben fortalecer el control de la salud y pasar del tratamiento a la prevención al brindar servicios a las personas mayores con afecciones crónicas. Además, las autoridades deben tomar medidas para alentar a las personas

mayores a ser socialmente activas y cuidar su salud. Como decíamos antes la sociedad debe decidir y elegir su modelo de desarrollo que seguro debe implicar, más digitalización, más emprendimiento, más energía barata para las personas mayores, más salud y dedicación a las personas mayores, etc.. Y sobre todo que genere empleo y dedicación satisfactoria a favor de y por la población adulta. En este sentido unas directrices políticas en materia económica, social, de infraestructuras, etc. bien dirigidas, serían las mejores herramientas para proponer soluciones y éxito en el cuidado e implicación de todos los colectivos afectados, sociedad en general y colectivo afectado de mayores.

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### Artículos importantes resultantes revisados y analizados

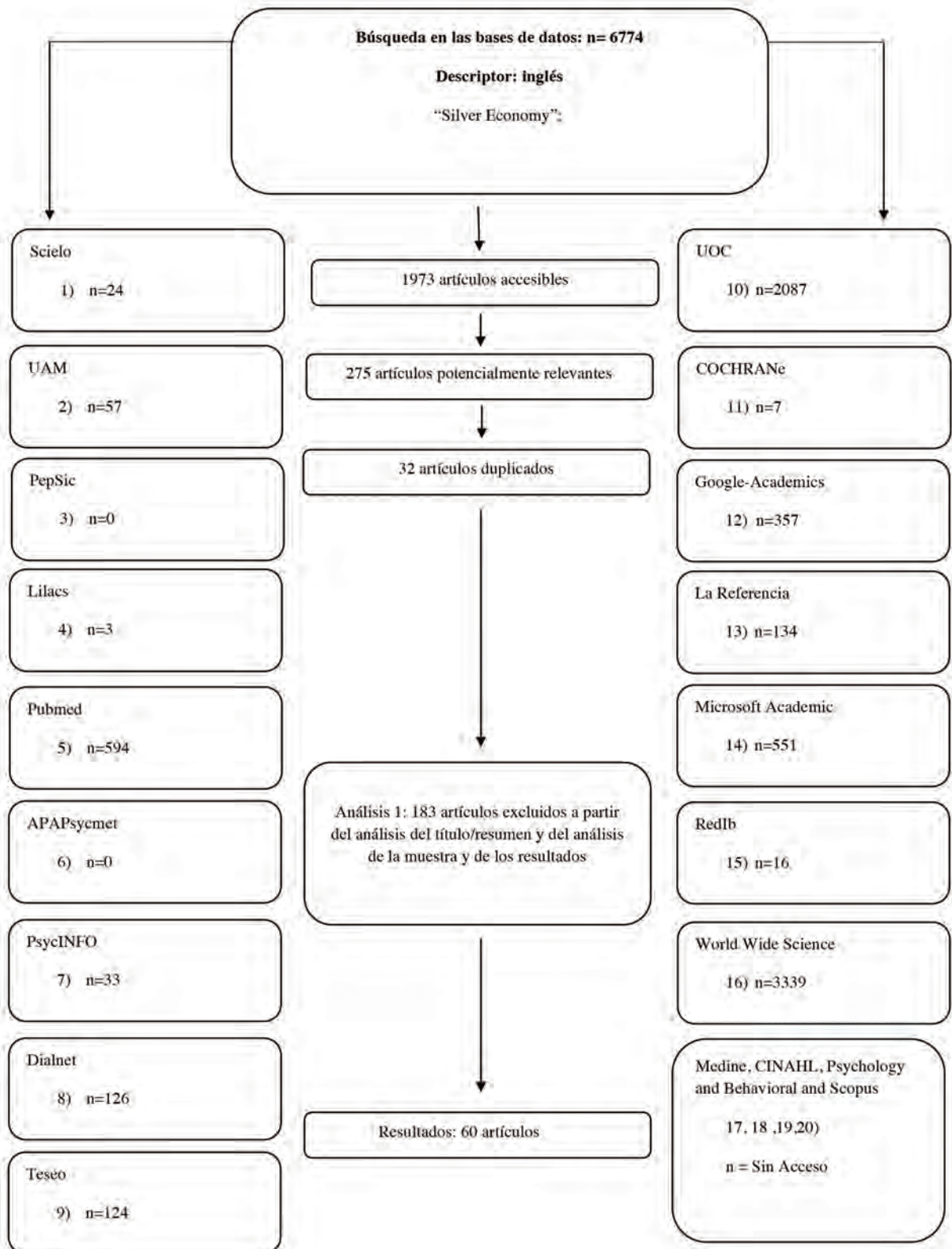
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ANNEX 1



# Rita Levi-Montalcini's first intellectual emigration and her research in the laboratory "à la Robinson Crusoe": the letters from Brussels and a "Wiggish" recollection

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**Abstract.** This article deals with the first part of the research eventually leading Rita Levi-Montalcini to her discovery of the Nerve Growth Factor (NGF), and particularly with the experiments carried out, in collaboration with her mentor, Giuseppe Levi, during the last world war period, in the laboratory as "à la Robinson Crusoe" that she had set up at her home in Turin. In her various recollections of the NGF discovery path, Rita regarded those experiments as an heroic and revolutionary research period of her scientific life. Nevertheless, at the time they did not appear to her innovative enough such to change immediately the ordinary research program she was pursuing in the pre-war period. We argue that Rita's narration of her initial experiments reflects a somewhat Wiggish attitude, and we discuss the possible reasons underlying her stance.

**Keywords.** Rita Levi-Montalcini, History of neurosciences, Giuseppe Levi, neuroembryology, Nerve-Growth-Factor, wiggish.

## La prima emigrazione intellettuale di Rita Levi-Montalcini e gli esperimenti nel "laboratorio alla Robinson Crusoe": Le lettere da Bruxelles e una ricostruzione di tipo "Whiggish"

**Riassunto.** Questo articolo tratta della prima parte della ricerca che ha portato Rita Levi-Montalcini alla scoperta del Nerve Growth Factor (NGF), e in particolare degli esperimenti condotti, in collaborazione con il suo mentore, Giuseppe Levi, durante l'ultima guerra mondiale, nel laboratorio "alla Robinson Crusoe" da lei allestito nella sua casa di Torino. Nelle sue varie ricostruzioni del percorso di scoperta dell'NGF, Rita considerava quegli esperimenti come un fase particolarmente eroica e rivoluzionaria della sua vita scientifica. Tuttavia, all'epoca in cui furono condotti, i risultati ottenuti non le apparvero talmente innovativi da indurla a mutare immediatamente il programma di ricerca ordinario che stava portando avanti nel periodo prebellico. Nella nostra opinione la narrazione che Rita fa dei suoi esperimenti iniziali riflette un atteggiamento *a posteriori* (di tipo in parte "Wiggish") di cui cerchiamo di analizzare qui le possibili ragioni.

**Parole chiave.** Rita Levi-Montalcini, Storia delle neuroscienze, Giuseppe Levi, neuroembriologia, Nerve-Growth-Factor, storia "Wiggish".

## La primera emigración intelectual de Rita Levi-Montalcini y los experimentos en el "laboratorio alla Robinson Crusoe": Las cartas de Bruselas y una reconstrucción de tipo "Whiggish"

**Resumen.** Este artículo trata de la primera parte de la investigación que llevó a Rita Levi-Montalcini al descubrimiento del Factor de Crecimiento Nervioso (NGF). En particular, se abordan los experimentos realizados - en colaboración con su mentor, Giuseppe Levi - durante la última guerra mundial, en el laboratorio "à la Robinson Crusoe" que ella instaló en su casa en Turín. En sus diversos recuerdos del proceso de descubrimiento de NGF, Rita considera esos experimentos como una fase particularmente heroica y revolucionaria

de su vida científica. Sin embargo, en el momento en que se llevaron a cabo, no le parecieron suficientemente innovadores como para cambiar de inmediato el programa de investigación ordinario que se estaba realizando en el período anterior a la guerra. En nuestra opinión, la narración de Rita de sus experimentos iniciales refleja una actitud *a posteriori* (en parte de tipo Wiggish) de la cual tratamos aquí de analizar las posibles razones.

**Palabras clave.** Rita Levi-Montalcini, historia de las neurociencias, Giuseppe Levi, Nerve-Growth-Factor, historia “Wiggish”.

*Rita and the dilemma of a young Italia doctor at the time of racial laws.*

In a previous article published in this journal, I have analysed the initial period of the neuroembryological researches carried out by Rita Levi-Montalcini at the University of Turin, at first in the Anatomical Institute and, afterwards, in the Clinic of Neurological and Mental Diseases, before her forced emigration to Belgium because of the so-called “racial laws” (1). As previously said, these laws, promulgated by the fascist regime in 1938, led to the expulsion, from the university, of numerous Jewish professors and students. Among the professors evicted was Rita’s teacher, Giuseppe Levi, one of the most prominent biologists of his era. Among the students or young researchers obliged to leave the University was Rita’s cousin and classmate, Eugenia Sacerdote, and Salvatore Luria, also a classmate in the medical course (who left Italy soon and would change his proper name in Salvador, once established definitely in the U.S.A.). Luria would be awarded the Nobel Prize in 1969 for his studies on bacterial genetics. There was, moreover, also Hertha Meyer, a young German laboratory technician (already mentioned in the previous article), from whom both Rita and Eugenia had learned the method of cell cultures *in vitro*. Hertha, who would leave Italy in January 1939 with the help of Rita, had arrived in Turin in 1933, on the run from her home country because of the German racial laws promulgated in 1933 by the Hitler regime. (see ref. 2)

When racial laws were decreed in Italy, Rita was conducting very promising neuroembryological research in the Neurological Clinic of Turin, in collaboration with Fabio Visintini, a young neurologist particularly expert of electrophysiology. (see refs. 1-3)

As mentioned in the previous article, Rita and Visintini were obliged to publish their paper *in extenso* in a Swiss scientific journal, because, among the many prohibitions imposed on Jew, there was also the impossibility of authoring articles published in Italian journals (ref. 4).

We have already said that, after the exclusion from the university, Rita considered various possibilities for her future life and research path. Being more



**Figure 1.** Léon Laruelle (1876–1960) was an important Belgian neurologist, the pupil of some great scholars of his time including the German Alois Alzheimer. In 1925, Laruelle founded a private institution in Brussels for the treatment of neurological diseases, It was in this laboratory that Rita conducted some of her studies during the period spent in Belgium.

or less equally attracted – as she would say in her later recollections – by experimental research and clinical practice in the neurological medicine, she considered the possibility of practicing private medicine (the only option open to Jewish doctors). Eventually she chose an opportunity offered by a Belgian institution where research and clinical practice went along, the *Centre neurologique* of Brussels, an establishment that – as the Turin Anatomical Institute – belonged to the network funded by the Rockefeller Foundation.

The *Centre neurologique* was a private institution founded in 1925 by Léon Laruelle, a clinician with strong interest into experimental science. It would become one of the main centres of the development of neurological research in Belgium. The decision of Rita, who was reluctant to leave the family for long periods and go to distant countries, was favoured by the presence in Belgium of her older sister Anna (Nina). Together with her husband, Ulrico Montalcini, and their three children, Nina had emigrated to Westende, on the Flemish coast. Moreover, also Rita's teacher, Giuseppe Levi, was staying in Belgium, although not in Brussels. Thanks to a grant of the Francqui Foundation of Brussels, he had been offered research facilities at the Institute of Pathological Anatomy of Liege directed by Jean Firket (see ref. 2)

*The letters from Belgium and a life commitment to experimental research*

Until very recently little information was available on the Rita's life and research on the period spent in Brussels, which lasted about nine months, from March until December 1939. In her main autobiography, *Elogio dell'Imperfezione* (written soon after the Nobel Prize award and published in 1987 – and afterwards translated into various languages) she did not deal with her experiments in Laruelle's institute (ref. 5). She dwells almost exclusively on the bad weather and the sense of anguish that dominated the Belgians on the imminence of a new war. This was sharply felt, particularly by the older Belgian people, those who had suffered the consequences of the German invasions a few decades earlier. Rita also alludes with a certain humour to her weekend visits to Giuseppe Levi in Liege, where the two used to make long walks

together, likely to discuss about science and the present political situation<sup>1</sup>

It is almost exclusively from the letters recently discovered by Piera Levi-Montalcini among the papers of her aunt that Rita writes to the members of the family remained in Italy (her mother, Adele, her brother Gino and her twin sister Paola) that we are now able to reconstruct some circumstances of this period in her life. Although – as we shall see now – the Belgian period was largely deceiving for the young scientist from the point of view of her experimental activity, it was nevertheless very important for her personal maturation, and especially for her professional orientation toward a life entirely dedicated to science.

In the first of these letters, dated May 29<sup>th</sup> 1939, and written from the house of Nina in Westende, Rita says that she had been the day before in Liège to meet Levi and show him her histological preparations. After reassuring the family about her health conditions, she adds that she will go as usual to the Institute (evidently the *Centre neurologique* in Laruelle) where “the work is going very well”. She adds that she has asked Visintini, her collaborator at the Clinic for Neurological and Mental Diseases, in Turin, to let the family have her “very delicate preparations”. These should be sent to her, appropriately packaged, in the trunk that the family is preparing for shipping. In the same trunk she asks, in addition to summer and winter clothes, some medical books, a clue perhaps to the fact that Rita intends to follow at least in part also the clinical activity that is component of the hospital routine of the *Centre neurologique*.

In the next letter, dated 30<sup>th</sup> July, and sent from Brussels, she says she had been in Paris, and – for the first time – she mentions “the Reumont”, that is Marguerite Reumont, Laruelle's assistant, with whom she is evidently about to collaborate in the experimental laboratory attached to the *Centre neurologique*. She

1 - In the *Elogio* Rita says that during the Belgian period she received every day a letter from a suitor Germano Rondolini, also a student in Levi's Institute, who had declared his love for her after the promulgation of racial laws asking her to marry him. It is possible that Rita, who was reluctant to accept the bonds of a marriage, had decided to emigrate also to avoid the prospect of an immediate engagement with him. Together with Rita's brother Gino and her twin sister Paola, Germano accompanied Rita on March 1939, in her emigration train journey to Belgium, as far as the France-Italy frontier in Bardonecchia.



**Figure 2.** A post-war photo that portrays Marguerite Reumont in her laboratory at the *Centre Neurologique*, together with a collaborator.

adds, however, that because of problems concerning the technicians, “the laboratory is in a rather shabby situation”. Rita then concludes by saying: “As for me, I expect to do just the bare minimum as I am far from the laboratory in spirit”. We do not know the reasons for this attitude, but it is certain that the research carried out in the immediately following period, in collaboration with Reumont, did not produce particularly significant results.

In the letter dated 21<sup>st</sup> July, the notes of pessimism on scientific activity are in fact more evident. Addressing herself in particular to her brother Gino, Rita writes: “enthusiasm has suffered a major collapse, and I have well-founded doubts about my scientific activity and the need for doing it”. She adds that “in any case” she has meanwhile “returned to the laboratory” (evidently after a prolonged absence, perhaps due – at least in part – to a recent trip to Paris). Then she writes:

In my absence, nothing, of what I had planned, has been done and therefore the work for Copenhagen will not be ready. At least as I had planned it. This has given me great peace and joy. Tomorrow I will see Laruelle

and we will see whether to participate anyway with what done until now. Very briefly, we plan to leave.

This is a significant passage, not only because it reveals Rita’s scientific difficulties during the period in Brussels, but also because it highlights an important aspect of the mentality of the true researcher: the anguish in the face of the difficulties of experimental work comes above all from feeling himself (or herself) personally inadequate and responsible for research failures. It is attenuated when the obstacles to its development come from external sources.

The reference to Copenhagen in this passage indicates the “III International Congress of Neurology” scheduled for August 21-25 in the Danish capital, an important event in which Laruelle and his collaborators intended to take part. On the problems connected with her possible participation in this congress, Rita returns in the following letter dated 4<sup>th</sup> August. Here she highlights the insufficiency of the results she obtained in the *Centre neurologique* for the purpose of presenting a scientific communication, with an evident criticism of Laruelle who – in her way of thinking – is at least partly responsible for the failure to complete Rita’s studies.

Here are her words:

I live in almost complete rest. Laruelle very kindly approved my decision not to make the communication since in this last period he has prevented me from concluding my research. Instead, I will make a demonstration of my preparations. For practical purposes, this is the same as a communication, but I will not compromise myself with assertions that I may later regret. I will give the full work at the next congress. You know how indifferent that is to me.

Rita then specifies that she will leave by boat from Antwerp on August 14<sup>th</sup>. Due to the large amount of histological preparations she will be carrying for the demonstration in Copenhagen, she would be driven to the embarkation city by the “Baroness”. The personage mentioned is Agnès della Faille d’Huyse, a Belgian aristocrat, acting chairman of the board of directors of the *Centre neurologique*).



**Figure 3.** Rita Levi-Montalcini, in a photo taken in Copenhagen during the Neurology Congress of 1939 (© Piera Levi-Montalcini).

The next letter was written from Copenhagen on August 21<sup>st</sup>, the day of the inauguration of the congress. In this letter Rita gives some details on the official ceremony that took place in the morning “with the intervention of the King” (Christian X of Denmark). The plenary lectures were given first by Henry Dale (who had received the Nobel Prize for medicine the previous year), and “immediately after, by Laruelle who has met with a lot of approval, and impartially it must be acknowledged that he has had a real success”.

Rita continues talking about the demonstration of her histological preparations, done together with Reumont, which has also been very successful, to the point

that Laruelle overtly demonstrated his satisfaction addressing her by saying repeatedly: *Ma chère amie*”.

It is singular that neither in the previous letters, nor in this one concerning the demonstration given to the Copenhagen congress, Rita specifies in any way the topic of the research she is conducting in collaboration with Reumont and under the direction of Laruelle. We have a very succinct account on the theme of this research from the conference Proceedings published in the *Revue neurologique*:

M. L. LARUELLE, Mlle R. LEVI-MONTALCINI and Mlle M. REUMONT (Brussels).

The vegetative centres of the spinal cord in mammalian embryos (cat and rabbit).

Communication essentially consisting in the presentation of preparations and projections; 1° on the first bud of the vegetative centres of the spinal cord in the rabbit embryo; 2° on the modifications, according to the embryonic development, of the three intermediate groups: internal, intermediate, intermediate-external; 3° on the characters of the cells and direction of the neurites of the three groups. (ref. 6, p. 369)

The theme of the demonstration represents a meeting point between, on the one hand, the interests of the group of Laruelle and Reumont, who for some years had been studying in particular the nervous centres of the autonomic system (sympathetic and parasympathetic) and, on the other, the skills and interests of Rita. As we know, in the period with Levi in Turin she had acquired a great experience in the manipulation of embryos, although her preferred preparation was the chicken embryo (while Laruelle and Reumont studied the mammals).

During the days in Copenhagen, an event of great importance for Rita was the encounter with Giuseppe Moruzzi, a young physiologist who had already acquired an international renown. This is what we learn from a conference Rita dedicated to Moruzzi in Parma on March 20<sup>th</sup> 1990, four years after the death of the great physiologist.

We first met at a conference in Copenhagen on a tragically historic day: it was the first of September 1939, the day of the invasion of Danzig. Moruzzi was



just one year younger than me, he was much more handsome and attractive, and I was impressed by the fame he had earned at only 29 years of age. I was a shy young girl who had recently graduated and I was perfectly unknown to him. For racial reasons I had been expelled, or – at least – obliged to leave my country and to take refuge in Belgium where I was offered work. On the day of our chance encounter in Copenhagen, the newspaper headlines were announcing the invasion of Danzig, which meant the beginning of war. We spent all day together [...]. He, like myself, was in a state of despair because of the alarming impending events, and I was struck by the serious way in which this young man faced them. Leaving aside my critical situation, the whole world was then in danger. All day along, until late evening, we discussed what could be done. Eventually, every one of us returned to their countries.[...] At that time, he was working in Cambridge with Lord Adrian; the importance of their studies was already known, as I will indicate later. I went to Belgium, and from Belgium I came back to Italy when the war was nearing, and then we all know what happened. By a miracle both of us survived and we were destined to meet each other ten years later.



**Figure 4.** A snapshot which shows Giuseppe Moruzzi, walking in Copenhagen in 1939, when he was attending the International Congress of Neurology in which he first met Rita Levi-Montalcini. (© Giovanni and Paolo Moruzzi).

(ref. 7, pp. 124-125)

To get a clue as to the reasons for the decisions that Rita made after returning to Brussels, it is necessary to take into account this meeting between the two young Italian scientists. Moruzzi was then working in Cambridge with the great English neurophysiologist Edgar Douglas Adrian (Nobel Prize for Medicine in 1932). In the immediately preceding years, however, he had spent a long period working in the Laboratory of Clinical Neurophysiology of the University of Brussels to conduct research under the direction of Frédéric Bremer (a physiologist then very famous for his studies on sleep mechanisms).

Back to Brussels, on 23<sup>rd</sup> September Rita writes to the family that she could not come soon to Italy due to difficulties in obtaining the necessary visa for the return. However, she does not approach this unexpected, and apparently annoying, situation with anxiety; on the contrary, she feels herself in a condition of “complete physical well-being”. In this letter, we find a notation that – in various forms – will come back the writings of her maturity. Rita narrates that she feels the scientific work as a delight, and – at the same time – as a way of escaping the worries of everyday life: “again I am very strongly attracted by my studies and I am amazed by the complete possibility of escaping to the present, diving into the wonderful charms of nerve conduction”.

What she then writes suggests a decision likely sketched during the meeting with Moruzzi in Copenhagen, and afterwards matured in Brussels, following the difficulties of returning to Italy and her uneasy situation at the *Centre neurologique*, where things have come back to the ordinary and boring routine, despite the success of the Copenhagen demonstration:

On Monday I hope to be able to speak with Bremer as I told you, to see if I can work with him. He is one of the most famous living physiologists and for this reason, it would be a great fortune for me to work under his guidance. If he accepts me, I will find myself in a more awkward situation than Buridan’s ass. The infinite desire to embrace you again pushes me to neglect the long-awaited possibility of continuing my studies; on the other hand, I am discouraged by the inactivity to which, on returning, I will have to face. If

I stay, I will most likely finish the work started in the Neurological centre but, as I told you, this work interests me much less than what I could do in Bremer's physiological laboratory. Therefore, if I am unable to work with him, I will also leave the work I started with Laruelle without much regret and will certainly decide to return.

Rita then asks her family for advice to help her in her decision, but she reassures her loved ones that, by staying in Belgium, she will not suffer loneliness due to the "infinitely dear closeness" of her sister Nina. Like many of the letters written from Belgium, this one also brings additions from Nina that fill in the empty margins left by the sister. Precisely because she imagines that the family in Italy welcomes with regret the news of the possible decision that Rita is taking to stay in Brussels, Nina intervenes on this point by writing:

Dear Ri [ta] is here reading next to me. I really wish she could remain. It is not selfishness, believe me, but I see that here she is so well, and that she is so animated for her studies that – I think – it would be really a pity to throw everything away now that we are more calm on the course done.

The next letter, dated 27<sup>th</sup> August, announces to the family the outcome of the interview with Bremer, which had been very positive despite the initially uncertain prospects outlined by the famous physiologist, due to the "greatly reduced subsidies to the laboratory" for which "it was very difficult for him to accept new applicants". The doors of the prestigious laboratory open wide for the young Italian scientist. With reference to Bremer, Rita writes:

He received me very kindly and I spent the morning with him. Result: he proposed that I definitely start working, and declared himself truly enthusiastic about the work program I presented him and about the work done in Turin. Today with the assistant, I have begun to sketch the research plan with an assistant.

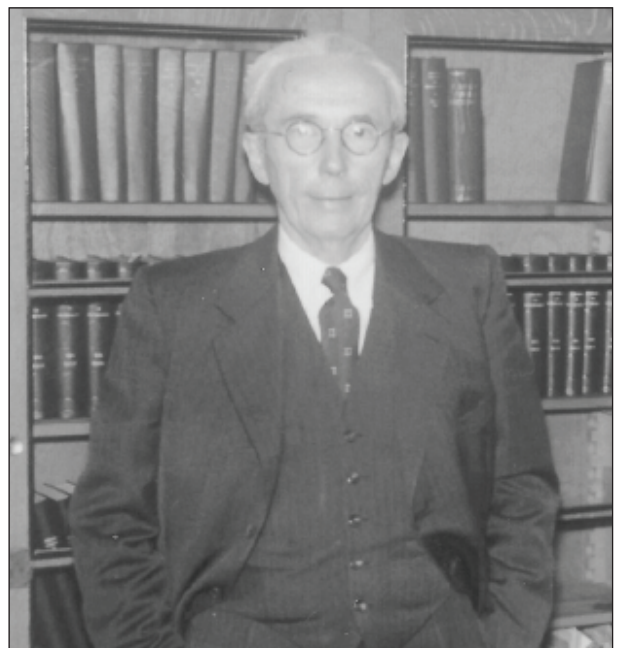
Nina intervenes again in this correspondence, undoubtedly to alleviate the disappointment of the family at the knowledge that, following acceptance in the

Bremer institute, Rita will probably remain in Belgium for a long time. With a certain humour she comments on the fame enjoyed by Bremer. Of him she says that he is "such a world celebrity that even the penguins at the north pole talk about him" [...] The fact that he has asked Rita to come to work with him immediately must make proud every maternal and fraternal heart. [...] If you could see her animated and full of strength as she is, you would rejoice with me".

On 6<sup>th</sup> October Rita writes again to the family saying, with reference to her new activity in the Bremer's Institute, that she spends "the afternoons in the physiology library, studying and dreaming of beautiful research plans, which perhaps will remain dreams, but that doesn't matter".

From the following letter, written on 11<sup>th</sup> October, we have a first indication of the work planned in Bremer's laboratory. This is evidently a research on chicken embryos, which, however, has a difficult start for the reasons that, she explains, with a certain humour:

I am now going to my laboratory where so far I have not been able to achieve anything because of the



**Figure 5.** Frédéric Bremer (1892–1982) in 1959 in his office at the University of Brussels. (© Giovanni and Paolo Moruzzi).

strike of my eggs, despite my cares more maternal than that of a hen. While waiting for the material, I spend my time studying in the library, where I find myself like a fish in water. The atmosphere is very pleasant.

The “strike” of the hens evidently ends quite soon, but new difficulties arise, as we learn from the next letter, dated October 15<sup>th</sup>.

Rita writes:

I attend the new institute assiduously but, up to now, embryos have played me bad tricks. Because of the malfunction of the thermostat, they all died before I could subject them to the experiment. Certainly, I am not discouraged for so little but I regret the lost time. The assistant and the technicians do their best to help me. I therefore hope to remedy this problem soon. Once overcome it, undoubtedly I will be confronted to more serious ones, given the difficulty of the experiences I am planning. I am – however – sufficiently stubborn and optimistic to face them.

The theme of the experimental difficulties with the eggs and embryos resurface in the following letter, written on October 15<sup>th</sup>:

Certainly I continue to fail with my eggs, but I am sure that sooner or later I will be able to overcome these stupid technical difficulties, and I am increasingly convinced that I have a very promising research field ahead of me. In addition, being able to work with Bremer is not only very pleasant for me but also very useful.

The next letter, written on November 15<sup>th</sup>, is dominated by preparations for departure which, however, cannot yet be undertaken because the visas necessary to cross the frontiers do not arrive (while the trunks are already ready). Rita too seems determined to return, following the advice received (in a previous letter) from Gino and Paola, but she cannot hold back her regret.

My Pa [ola]- and Gi [no], I listen to your advice, and I leave my chicks and – with them – all my

dreams of working in the best laboratory I have found so far. My dearest ones, you will forgive me this regret, which may appear to you excessive. But, in recent months I have been through such painful moments, and I owe to this new activity – just begun – to have acquired serenity and confidence in the future. I hear my dear Gi [no] all your just objections, summed up in the detachment of the Demiurge from the troubled human affairs. Working happily without becoming slaves! Very sensible thinking, but which does not take into account the affective component of human nature. That should not be ignored too much, because – after all – it is the mainspring of all our activities and its justification.

She expresses also her regrets for not having been able to complete her research at Laruelle’s laboratory.

In the last letter sent from Belgium, dated November 17<sup>th</sup>, Rita seems to reconsider her decision to return soon to Italy, and outlines the possibility to stay another month in Brussels, in order to continue her physiological experiments, if in the meantime Bremer returns and the laboratory will be back in function. Returning home attracts her because of the possibility of hugging family members to whom she is very attached. Rita realizes – on the other hand – that in Turin she will have to face “the certainty of a situation of complete inactivity”. In contrast – as she says – in Bremer’s laboratory “I saw all my work projects come true”.

The letter ends with Nina’s usual addition, this time entirely dedicated to her sister’s condition of anxiety and indecision. It is worth transcribing it in full, also because it contains a reference to Rita’s adolescence, at the time of the girl’s decision, – against the will of the father, Adamo Levi – to resume her studies in order to have to access a professional career, a possibility generally precluded to young women:

My most beloved ones, there is no doubt that for now there is no longer any reason for apprehension here, and that perhaps Ri [ta] could still stay for a while – even if we can leave – which is not yet certain. I hope you have received our last letter, in which we talked about this possibility, and that this letter will find you prepared. It would be a matter of enabling

Miei amichissimi, non c'è dubbio alcuno che per ora qui non ti resti  
 più alcuna ragione di apprensione, e che forse Rita potrebbe ancora  
 fermarsi un poco - anche ammetto che voi ti potete partire, il che  
 non è ancora affatto accertato - Però avete ricevuto l'ultima vostra  
 lettera, nella quale ti parlavo di questa eventualità, e che lei presente  
 ti... non preparati - E' batterebbe di darle modo di recuperare qui  
 quanto ha temuto fin'ora, ha da Bremer che al Centro, e soprattutto  
 ho di non darle un brutto dispiacere. Ritornerebbe a Torino, al più tardi  
 entro Dicembre, carica di allori e di titoli per l'avvenire - Già  
 solo l'idea di riprendere il tuo lavoro te ha fatto riflettere il tonito sulla  
 labbra e... te ha rivoltato a posto lo stomaco che in questi giorni  
 non andava momentaneamente troppo bene - Il lavoro è veramente per  
 lei ragione di vita, e forse la sola ragione, te ti eccitava il grande  
 attaccamento per noi e per voi. Ho pensato che, se il caso ripa-  
 rava un tantino, avrebbe ancora una volta che "la nostra" come  
 mi disse in quel memorabile giorno in cui te sfalleggiavi - e me  
 ne vantavo - a riprendere gli studi - Il mio grande affetto per lei mi  
 garantisce che, se qualche cosa faccio o dico, lo faccio esclusivamente  
 te per il tuo bene, anche a costo di prendermi qualche piccola  
 grande responsabilità. Mi perdolate, miei adorati.

**Figure 6.** The addition by Nina Levi-Montalcini to Rita's letter of November 17<sup>th</sup> 1939 in which the Nina remembers her intervention of many years before in support of Rita's decision to continue her studies with the aim of going to the University and accessing a profession (© Piera Levi-Montalcini).

her to reap here what she has sown so far. Both at Bremer and at the Centre, and, above all, not to give her a big disappointment. She would return to Turin by December at the latest, full of laurels and titles for the future. Just the idea of resuming her work made her smile again on her lips and ... put her stomach back in place, which was not going too well these days. Her work is truly her reason for living, and perhaps the only reason, except for her great attachment to you and to us. I am thinking that, if our dear Dad heard me, he would say, once again, that "I put her up", as he said me on that memorable day when I supported her – and I am proud of that – to resume her studies. My great affection for her guarantees me that anything I do or say, I do it exclusively for her good, even at the cost of taking on some small-great responsibility. Will you forgive me, my beloved ones?

We do not know if Rita and her sister's family eventually could get the visas necessary to cross the frontiers and come back home. However, as narrates recounts in her autobiography, they succeeded in arriving to Turin, just on Christmas Eve 1939, after a lengthy and rather adventurous car journey, through the Europe devastated by the war. (Levi-Montalcini, 1987).

In conclusion, the months spent by Rita in Belgium represent a period of strong anguish and bitter disappointments. In neither of the two laboratories attended, was she able to conclude satisfactorily the research undertaken. At the *Centre neurologique*, where the study project was a rather conventional histological research, she certainly had difficulties, even of a personal nature, at least in the relationship with Laruelle



**Figure 7.** A pencil portrait of Anna (Nina) Levi-Montalcini made by her brother Gino in 1959 (© Piera Levi-Montalcini).

(and perhaps also with Reumont). Certainly, in the letters she writes, there was never any sign of appreciation for them from the human point of view. She is much more enthusiastic about Bremer, his lab, his personality, and even the research project she intends to develop with him (almost certainly based on an electrophysiological study of the developing nervous system in chicken embryos). A project that probably was linked to the one she had conducted in Turin together with Visintini, and which – as we know – she had been forced to abruptly interrupt due to racial laws, but which could have been developed in Brussels in one of the most important electrophysiology laboratories of the world.

On the other dimension, the Brussels period is extremely beneficial for Rita's scientific and personal life. It is there that her vocation for experimental research becomes well defined and clear-cut, while – in the initial period of studies and investigation in Turin

– she was divided between medical practice and laboratory research. As we have already noted, – at the time of her forced emigration, the attraction for clinical medicine had perhaps directed her towards the *Centre neurologique* of Laruelle, rather than toward a basic research institution. Rita's vocational maturation is also evident from the stubborn confidence with which she faces the difficulties that hinder the course of her experiments (at Laruelle's there are no good technicians, at Bremer's the embryos die perhaps due to the malfunctioning of a thermostat) and – from her attitude toward the greater difficulties to come.

*The return to Turin, and the advice of a new dantesque Ulysses, Rodolfo Amprino*

As she was anticipating, discouragement and frustration for the forced scientific inactivity were the sentiments dominating Rita's mood for a long period after coming back to Italy. This situation, however, will end about one year later, following a rather unexpected encounter with a former colleague at the Anatomical Institute of Turin, Rodolfo Amprino.

Rodolfo, who was not Jewish, had left Italy after the racial laws. This was because, as other loyal and affectionate collaborators of Giuseppe Levi, he was disgusted by Levi's dismissal. Moreover, he was nauseated by the attitude of the new director of the Institute, Ferdinando Rossi, a decidedly mediocre anatomist, very close to the fascist regime. After a period spent in a laboratory in Chicago, Rodolfo had come back to Italy, and eventually, on November 1940, he visited Rita in her home at Corso Umberto of Turin.

In the *Elogio* Rita describes, with a certain emphasis her encounter with Rodolfo, who unexpectedly went to ask her “in a rough way ‘à la Piemontese’ about her [scientific] projects”. Surprised as she was by Amprino's inquiry, Rita says that she was not able to reply promptly.

And adds:

My silence provoked his abrupt and somewhat irritated reaction: ‘you don't lose courage in the face of the first difficulties. You should set up a small laboratory and resume the interrupted research. Remember that

Cajal, in that sleepy city that must have been Valencia in the middle of the last century, built a fundamental work that laid the foundations for everything we know about the vertebrate nervous system'. The suggestion could not have fallen into more prepared ground to receive it. At that moment, Rodolfo appeared to me in the guise of Ulysses, as Dante immortalized him in the XXVI canto of the *Inferno*, when he encourages his companions not to lose heart and to continue the route. In fact, he touched a chord that had vibrated in me since early childhood: the desire to explore unknown places and adventures. The jungle that presented itself to me at that moment was more fascinating than a virgin forest: it was the nervous system, with its billions of cells, aggregated in populations, each different from the other and locked in the apparently inextricable tangle of nervous circuits, intersecting themselves in all directions inside the cerebrospinal axis. Added to the pleasure I anticipated for that type of studies, there was the idea of carrying out the project in the prohibitive conditions created around us by the racial laws. If Cajal, with his giant moves and his exceptional intuition, had dared to enter that jungle, why not venture myself into the road opened by him? The first experience with Visintini had been very encouraging. (ref. 5, p. 94).

This long quotation is a typical example of the rather epic way in which, in her later recollections, Rita narrates some crucial moments of her life and experimental research during the difficult period of the war. It is written with a certain literary taste, and, in addition the reference to Dante, is largely inspired by the writings of Santiago Ramón y Cajal, the great Spanish neuroanatomist, who was also a very effective writer. Indeed Cajal's autobiography (*Recuerdos de mi vida*), published in various editions, starting from the 1920s (and translated into various languages), had become a *livre de chevet* for many young scientists of the time. Applied to the description of the minute anatomy of the nervous system, the expressions used by Rita such as "jungle", "virgin forest", "apparently inextricable tangle" undoubtedly resound of some splendid passages of Cajal.

The *Elogio* was written between 1986 and 1987, and certainly reflects the state of mind of Rita after

the Nobel Prize was awarded. An important reference to the meeting with Amprino, less literary but no less significant, is present in a letter that Rita wrote to Rodolfo on February 14<sup>th</sup>, 1974, with a precious indication that allows us to establish the day of the event:

The racial laws prevented me from attending the Institute, where, on the other hand, Rossi reigned. And I remember that evening when you came to me (the same day your Father died almost suddenly) and you convinced me to organize a tiny laboratory in the house. The rest was only the consequence of your suggestion (how many times have I thought about it and with what gratitude!) and of the courage you have been able to infuse me with your words.

Lorenzo Amprino, Rodolfo's father, died on November 13<sup>th</sup>, 1940, and therefore – if we can trust Rita's memory (very strong, but not infallible) – then the fateful encounter, a true "turning point" of her scientific activity (as, in her letter, she defines it using the English phrase) is to be placed in the evening of this day. A day that takes place in a rather sad period for Italy, which has recently entered the conflict, after the declaration of war on France in June 1940.

*Planning a home laboratory: an affluent Jewish family and the "casalinghitudine"*

We know that Rita followed Amprino's advice, and that this had extraordinary consequences on Rita's future scientific career. At the time it was made, the decision to create a home laboratory for the investigation of the nervous system in the chicken embryo must undoubtedly have appeared rather unrealistic and somewhat reckless, especially considering that it was taken by a family group consisting largely of women. Rita's father, Adamo Levi, had died in 1934 and the family was made up by her mother, Adele Montalcini, by Gino (the eldest of the children), and then by Anna (Nina, who was – as we know – married), and by Rita and her twin sister Paola. In her recollections, Rita writes that Adele had supported the choice, even if it involved significant financial costs, the most significant of which was the purchase of two Zeiss microscopes, one with low magnification for microdissection, and the other with high magnification objectives, needed

for the observation of histological slides. Gino (the first to add the mother's family name to the father's) was an architect and had great technical-manual skills. He built "a thermoregulated glass box", with two openings that allowed the experimenter's arms to be inserted in order to operate the embryos in an aseptic environment. This was a simple and appropriate substitute for the sophisticated culture chamber used by Rita in the anatomical institute of Turin for the studies of cell cultures, since the period of her graduation. She had been working in collaboration with her cousin and classmate Eugenia Sacerdote, under the supervision of Giuseppe Levi and Hertha Meyer. The letters from Brussels suggest that, although living in her own home, with her husband and children, also Nina undoubtedly supported Rita in her decision to set up a home laboratory.

To understand how, in the case of Rita, it was possible to implement materially Amprino's suggestion of

building a home laboratory by a predominantly female family group, we must consider the importance of women in families of Jewish descent. We must also take into account the importance of the home interior as a place of intensely lived life and a space for creativity. This is along the idea of "*casalinghitudine*" (from "*casa*", home), a word created by Chiara Sereni to indicate the deep affection of Jewish families for the interior of their homes, the sense of protection they felt therein, and also its conception as a place for creativity, matured especially at the time of confinement within the ghetto (see refs. 8-9). We must also consider the fact that the Montalcini were a wealthy family and could easily afford the large costs of buying expensive microscopes and other laboratory equipment. Among other things, they owned the building in Corso Umberto where many members of the family lived, and in which Rita was able to set up a first laboratory and start her research destined to have truly extraordinary developments.

The laboratory was eventually installed in Rita's bedroom. It became soon a meeting point for her friends and colleagues that were against the fascist regime. Starting from the summer season of 1941, in her work she was helped by Giuseppe Levi. The authoritative and rather imposing master was now in the minor position of Rita's assistant, as he would recognize in a letter to Viktor Hamburger (Rita's mentor in the first years of emigration to the Washington University of St. Louis).

In this letter (written in German on 11<sup>th</sup> March 1959, in order to acknowledge Hamburger's contribution to the celebration of his 85<sup>th</sup> birthday), Levi says:

It is especially flattering for Rita and for me that a researcher like you, who is considered a great authority in the field of developmental physiology, has appreciated our findings. But I must confess that in those investigations published in 1942 my personal participation was very slight. They were done in the private apartment of Rita. I was just back from Belgium where I had undergone difficult events.

With the events of the war becoming more and more threatening for the inhabitants of Turin, from the house in Corso Umberto the laboratory would be



**Figure 8.** A photo of 1940 with the family group who decided to set up an experimental laboratory in Rita home in Turin. From left to right: Gino, Rita, Adele and Paola Levi-Montalcini (© Piera Levi-Montalcini).



**Figure 9.** A portrait with dedication donated by Levi to Rita on 25<sup>th</sup> July 1943, the day after the meeting of the Grand Council of Fascism which decreed the end of the dictatorship of Mussolini, and brought hopes, immediately disappointed, in many Italians on a possible return to normality (© Piera Levi-Montalcini).

eventually transferred to Valle San Pietro, on the hills near Asti. It was installed there in the house owned by the Nina's husband, Ulrico Montalcini (Villa Agnelli), where part of the family had taken refuge to escape the heavy bombing of the city. In that period, Rita used to come to Turin to meet Levi and discuss with him about the experiments and the way to publish the results she was obtaining. This situation lasted until the end of 1943, when – following the German invasion – both Rita and Levi (with their respective families) were obliged to go away and look for a refuge toward the south of Italy.

The research Rita carried out in her home laboratory is really of great importance and marks a change of paradigm in the history of neuroembryology (in

the meaning of a famous book of Thomas Kuhn, see ref. 10). With no doubt these experiments of the war period set the stage for the future investigation of Rita, largely carried out in St. Louis, leading her and her collaborator, Stanley Cohen to the Nobel Prize.

It is not surprising, therefore, that, in her autobiographical recollections, Rita gives a particular emphasis to the history of that period of her research. She narrates the experiments with literary taste, starting from the period in which they were planned, i.e. following the reading of a paper by Viktor Hamburger, her future mentor – as we know – in St. Louis. Rita portrays the results obtained as a heroic and revolutionary achievement, and the beginning of an uninterrupted, fascinating and epic, research pathway, concluded many years afterwards with “the honours of Stockholm”. However, as we will now argue, this is not exactly the way she felt at the time she was working in her home lab, nor in the immediately subsequent years, until her emigration to St. Louis. Many clues suggest that the way she narrates the beginning of what she will call the “NGF Saga”, is largely based on a *posteriori* attitude (“Whiggish” according a particular acceptance of this abused word). An attitude that was the consequence of the unpredictable extraordinary developments of her 1944 experiments, and also of Rita's new situation after the NGF discovery and – especially – the Nobel prize award.

In order to clarify this point I need to summarize and discuss here the experiments carried out by Rita and Levi during the war period, and to situate them in the appropriate historical context of the ongoing development of neuroembryology. For a more detailed account, the interested reader is referred to a recent book in which I have analysed in detail the beginnings of Rita's scientific activity.

#### *The chicken embryo, Maria Lydia Shorey and the birth of modern neuro-embryology*

The research topic along which the discovery of the NGF lies corresponds to one of the fundamental problems faced by scholars since the introduction of experimental methods in the field of neuroembryology. It concerns the mechanisms that regulate, during development, the establishment of contacts between nerve cells, and between these the organs and tissues



they innervate, both on the motor and sensory side.

A landmark study in this research path appeared in 1909, the year of Rita's birth. The author was a young American researcher, Marian Lydia Shorey, and was based on her doctoral thesis, developed under the supervision of Frank Rattray Lillie at the Department of Zoology of the University of Chicago (ref. 11). Lillie, who had been one of the founders of the Marine Biological Center in Woods Hole, was an authority on developmental biology. He had been instrumental in contributing to introduce, in this research field, the chicken embryo as a reference preparation, especially with the publication, in 1908, of the volume, "*The development of the chick, an introduction to biology*". In this book, against a consolidated tradition of research based mainly on morphological investigations, the American scholar promoted a dynamic and physiological vision of the study of development, largely based on experimental manipulations, which he defined as "developmental physiology" or "experimental embryology" (12).

Among the fundamental factors that underlie embryonic development, Lillie considered, particularly "the effects of the intraorganic environment, *i.e.*, of component parts of the embryo on other parts", which he indicated as "correlative differentiation". Against a preformistic conception of embryonic growth, he assumed that – far from being programmed in every detail – the harmonic growth of organs or parts of organs is based on the reciprocal influence of neighbouring structures or in functional relationship. This integrated or "correlated" action is mainly the outcome of influences exerted through the extracellular environment.

Within these conceptual frameworks, in her PhD research carried at the University of Chicago under Lillie's supervision, Shorey conducted a series of experiments aimed at investigating the effects of removing peripheral structures on the development of nerve cells of the spinal cord. Using fine sewing needles as electrocautery devices, she destroyed the buds of one of the two wings in the embryo (leaving the other intact as a control). Shorey found that this manoeuvre led to a reduction in the number and size of the precursors of nerve cells (neuroblasts), in particular in the motor columns of the spinal cord and in the corresponding sensory ganglia, (*i.e.* those normally assigned to the



**Figure 10.** Marian Lydia Shorey (1873-1922). Graduation photograph from the Eastern State Normal School of Castine (Maine), 1894 (©).

motor or sensory innervation of the wing). Based on a series of considerations, she interpreted these effects as due to a failure of nerve cell growth (hypoplasia), due to the lack of some influence, normally exerted by the peripheral tissues through the extracellular medium (lymph), and absent following the destruction of the wing buds.

#### *Spemann's pupil and an article read in a cattle car*

In 1932, about twenty years after Shorey's fundamental work, one of the students of the German embryologist Hans Spemann (who will receive the Nobel in 1935), the aforementioned Viktor Hamburger, received a fellowship from the Rockefeller Foundation to conduct research in Chicago, in the Department of Zoology headed by Lillie, Shorey's mentor – as we

know – in her doctoral dissertation. On Lillie's suggestion, Hamburger repeated Shorey's experiments on chicken embryos, using the more refined methods used by Spemann and collaborators in amphibians. In 1934, Hamburger published an article, largely confirming and expanding Shorey's findings, which is particularly important to the story of NGF. This is because a copy of this work was sent by the author to Giuseppe Levi, who passed it to Rita in 1938, asking her to read it carefully and possibly check the results and conclusions. The exchange of publications between Levi and Hamburger was favoured by the fact that they were both members of the network of European scientists funded by the Rockefeller Foundation, which was then engaged in an effort to promote biomedical research worldwide.

Rita has narrated the moment in which she first happened to read Hamburger's 1934 paper at length and with emphasis, at least in two occasions. One was in relation with the celebration of Viktor's 80<sup>th</sup> anniversary. The written text, published in 1981, deserves an extensive quotation, both as an example of Rita's literary talent, and also because it is relevant to the point I am raising:

I first met Viktor in a cattle car in northern Italy. It was on a day in that fateful June of 1940 when Mussolini declared war against France, which had already been stabbed to death by Hitler's army. Sharing a train with cows was only a minor discomfort compared with those about to afflict the daily life of the Italian nation throughout a catastrophic five-year war. But, in mid-summer of 1940, Il Duce was triumphantly predicting "instant victory" over loudspeakers that blared from the Palazzo Venezia.

I was sitting on the floor of one of those railway cars, which have neither seats nor side walls with conventional doors (niceties unknown to cows) and my legs were dangling out in the open air. The train was running at a slow speed across the country between Turin and the small village I was heading for. I was young and I enjoyed the fresh air and this rather unusual and somewhat dangerous way of travelling. While contemplating the yellowing corn and the bright red poppies, I was reading a reprint lent to me by Giuseppe Levi on the effects of wing bud ex-

tirpation on the development of the central nervous system of chick embryos. The article was dated 1934, and as Levi had informed me, it had been written by a pupil of Hans Spemann. In the eyes of Levi, who was a great admirer of Spemann, this was the main, if not the only, merit of the article. I confess that I started reading it with only lukewarm interest, being more fascinated by the beauty of the passing scenery than by the account of the changes called forth by intervention in the developing nervous system of the embryo; but the crystal clarity of the writing slowly prevailed over my admittedly never-too-strong feelings for rural life. I could certainly not have anticipated on that day the far-reaching consequences of this first encounter with the chick embryo-and with Viktor. Though I was to meet the former in the flesh on subsequent days, seven years were to elapse first – and many extremely traumatic experiences were to be endured – before I actually met Viktor. By that time, I had learned a great deal about the chick embryo though nothing about Viktor. He had remained for me, until the day of our first personal encounter, "one of Spemann's pupils," according to Levi's definition which spelled out in these three words his admiration for "Spemann the Master" – and his concept that a pupil is simply a master's hand with no brain of its own. (ref. 13, pp. 22-23)

In the very similar narration of the episode Rita gives in 1987, in the *Elogio*, there are small but significant differences. Some of a literary type, such as – for example – the fact that he does not explicitly mention the "yellowing corn and the bright red poppies" (she simply says: "I enjoyed the view"). She adds instead the reference to the "hay-smelling" air, which is repeated twice, in a slightly different form (on p. 98 and p. 99) and serves, a bit like Proust's madeleine, to mark – with the most engaging force of the olfactory sense – a memory destined to significantly affect her life. Another minor difference is that, in the 1987 narrative, Rita makes it well clear that in that distant circumstance she was not actually travelling in the company of animals, but was simply in "a waggon that carried cattle before the war". Another small difference is that in the second narrative Rita says that she was travelling in the company of a suitor, Guido, noting how his "watchful hand" helped to guarantee her "from pos-

sible falls”.

More important is the absence in the second narrative of the critical reference – and certainly ungenerous and almost malevolent – to the fact that Levi considered a pupil nothing more than a manual instrument at the disposal of his teacher, almost lacking any thinking ability of his own. A statement completely contrary to the reality of the facts, and also to the memories of the students (including Rita herself in other places and times), since all concurs to underline Levi’s profound respect for his students and collaborators. If Levi really hinted at Hamburger’s article with some disdain, it is possible – as we will see better later – to find a scientific, and not trivial, explanation for his attitude. In fact, a master of the study of the nervous system of his level certainly could not appreciate, at least from a methodological point of view, a research like that of the young German scientist, based – as we will now see – on the use of staining techniques totally inadequate to mark nerve cells. A research, in which – according to Levi – in choosing the most suitable structures for his neuroembryological study, the author seemed to ignore even “the reasons well known by every histologist” (ref. 14, p. 539).

The reason for the absence, in the *Elogio*, of Rita’s criticism of Levi, as a poor estimator of the students intellectual abilities, is easily accountable for. It has to do with a chapter of the book, entitled “*Farewell to a teacher and a father*”, which is dedicated to Rita’s last meeting with Levi. This event took place “on an evening in late January 1965, at the San Giovanni hospital in Turin”. The teacher was then hospitalized for gastric cancer – and also for gangrene in his right foot, which was then extending to his leg – two conditions that would lead to Levi’s death within a few days (on February 3<sup>rd</sup>).

In her engaging and sympathetic narration, Rita recalls, together with Levi, the “joys and bitterness” of their intense life, the researches, the difficult moments of racial persecutions, their emigration to Belgium and the return in difficult circumstances, the experiments made together in her home laboratory in Turin. Faced with the intellectual vivacity and still youthful enthusiasm for science of the old professor (Levi was 92 years old), Rita says that she “understands the secret of the great influence he exercised on young

people”. This derived from “the passion with which he had pursued his studies and directed those of his students, indifferent to the honours and applause paid to the old masters”. Compared to the deep appreciation of Levi in the “Farewell” chapter, a critical reference to Levi as poor estimator of the students in other parts of the book, similar to the 1981 narration of the “cattle car” reading, would have been ill placed in the *Elogio*.

With regard to this rather significant discordance between the two narrations of the event, it is significant to note that is rather common for Rita to present narrations or express judgements which can be significantly different in written or oral texts produced in various moments of her long life. Although, this can be due to rather comprehensible and ordinary reasons, there is no doubt that often she adapts with skilfulness to the circumstances, and somewhat opportunistically manipulates, her accounts of the facts narrated. As to Rita’s criticism toward Levi’s attitude with students and collaborators, although the master was known, both in family and in the laboratory for its “terrible fits of anger”, generally due to “his intolerance of the superficiality and failure to fulfil the duties entrusted to them to them”, he had a profound respect for their work and their personality. In fact, few Italian academics respected so deeply the work of students like Levi, who constantly wanted their scientific results to be published in their exclusive name, and was always prodigal of advices and helps towards students and collaborators.

#### *Viktor Hamburger and the renaissance of modern neuroembryology*

It is time now to go into the specifics of the Hamburger article, which Rita had read in such particular circumstances narrated with great vivacity (15). This article represents a milestone in the history of neurobiology, despite some undoubted flaws in the experimental approach of the young German scientist, properly emphasized by Rita and Levi in their 1942 paper. Rereading what Hamburger wrote, even many years later, it is easy to agree with Rita when she speaks of “the crystal clarity of the writing”. In fact, there is a profound rigor and systematic organization in his interpretation, analysis and discussion of the results, and in the planning of the experiments. These qualit-

ies must have attracted Rita when she read the article, in the phase of forced experimental inactivity she was then living.

As said, Hamburger carried out his experiments in Chicago, upon Lillie's suggestion, as a check and extension of those made by Shorey in the same lab about 20 years before. He fully confirmed the previous results, with experimental concordances in some cases rather surprising, for a research made many years later, with somewhat different techniques and open to different sources of variability and uncertainty. The reduction in the number of motor cells induced by the ablation of the peripheral structure was similar. As Shorey, Hamburger also obtained a reduction – albeit less significant than his predecessor – in the development of the sensory nerves and ganglia, and of the sensory component of the spinal cord. Furthermore, using – like Shorey – a staining method based on a haematoxylin-type colour, he agreed with her in asserting on the lack of degeneration phenomena in the spinal cord, and – attributing the observed effects to a hypoplasia consequent to the removal of peripheral structures.

The difference between Hamburger and Shorey concerned mainly the interpretation of the effects observed. This depended on an aspect that the German scholar emphasized in his paper. The degree of hypoplasia observed in the spinal nerve cells did not exclusively depend in a quantitative way on the mass of the removed peripheral structures. It had also a qualitative specificity, in the sense that there was more marked hypoplasia in the motor cells of the cord if the removed part contained a greater muscle mass. If more proportion of the skin was removed, the hypoplasia concerned more the sensory structures.

Based on these observations, Hamburger considered unlikely an explanation – as that invoked by Shorey – relying on a generic chemical-metabolic action exerted by peripheral structures on spinal nerve centres. A metabolic action should be substantially non-specific, while – he says – “the different centers within the nervous system react in a very specific way, each one typically different and independent of the others” (ref. 15, p. 472). He then rejects (perhaps in a not entirely justified way, at least with hindsight) the idea that a way to account for the specificity of the central nervous effects “would be to ascribe to each

center its own intrinsic, characteristic manner of reaction” (*ibidem*). Finally he considers also untenable the idea that the central effects can be explained as a consequence of a reflex action, through the activation of sensory fibres, on the basis of the observation that they also persist in embryos in which the sensory fibres have been removed.

Having excluded various possibilities, Hamburger eventually proposes his own interpretation. The stimulus acting on the spinal cord, and responsible for nervous development, is carried by a particular type of sensory fibres that would act as “pathfinders”. These fibres would come into early contact with the corresponding peripheral tissues, and would then somehow transmit the stimulus responsible for growth to the nerve centres.

This is how he puts it:

We must charge the end organs of these first pathfinders with the double task of locating the peripheral field, and, in some way, ‘reporting’ back centripetally to the central organ the approximate size of the field to be innervated. The fibers would communicate the result of their exploration to their own cell bodies which thus would become the first relay station for the stimulus to be transmitted. Under the influence of the stimuli these nerve cells, which are not yet fully differentiated, when they have sent out their axones, would undergo a morphological or physiological change. (*ibidem*, p. 475)

In this way the German scientist excludes any chemical action based on a diffusible chemical agent and outlines an explanation which contains *in nuce* a hint to the axonal transport still to be discovered.

*Rita and Levi, the silver impregnation and the obsession with “cell count”.*

These are the results and the conclusions contained in Hamburger's 1934 article that, many years later, Rita would qualify of “crystal clarity” for the way it was written, an article that acted soon as a stimulus for her researches in the home laboratory that she was then setting up. In collaboration with Giuseppe Levi, she carried out a series of experiments on the effects of peripheral ablation on the development of the chicken nervous system aimed at verifying Hamburger's data

and interpretation. There are two main reasons why the reading of this article acted as powerful stimulus for Rita's (and Levi's) research. One had to do with the long lasting interest existing in Levi's laboratory in the themes of the growth of the nervous system and the development of connections between nerve cells, and between these and the tissues innervated by them (muscles, glands, cells of various kinds: see ref. 2) Another – and important one – was that Hamburger's article was somewhat connected to the neuroembryological research that Rita had been pursuing in collaboration with Visintini. It did not require, however, the sophisticated electrophysiological apparatus available at the Neurological clinics, an apparatus that was absolutely out of the horizons for her home lab.

Rita and Levi studied the problem investigated by the German scientist from a slightly different point of view, and – importantly – with partly different and certainly more effective methodologies. Their approach was nourished by the rich neuro-histological background of Levi's school, and was based on a severe scientific attitude that the master had followed since his studies at the University of Florence initiated in the last part of the nineteenth century.

In the wake of a long tradition, in order to stain nerve cells, Levi and his collaborators used the metallic impregnation techniques discovered by Golgi in 1873 (and subsequently varied and used with great success by Santiago Ramón Y Cajal and his pupils – including Fernando Castro who had worked in the Levi's institute in 1934: see refs. 17-18)

Another important attitude that Rita had derived from Levi was the habit of extreme precision in the collection of experimental results and – in particular – the custom of measuring the size of cells and counting their number. Rita is often quite critical, and at times decidedly ironic, about the master's obsession for the precision of measurements that led sometimes to very boring tasks for his collaborators. Indeed, the first research project, that she and her cousin Eugenia were assigned by Levi, consisted in counting the number of nerve cells of the sensory ganglia in the spinal cord of the house mouse (*Mus musculus*). The aim was to ascertain whether the number was rather constant or more or less variable (19, see ref. 2).

As one can easily imagine, the work, which re-

quired the total count of over three million nerve cells, turned out to be “very tedious”, and certainly did not seem to the two cousins so important as to justify the hard fatigue required. In spite of this, the experience acquired with this research (the basis of the first article published by Rita and Eugenia in 1934, two years before their graduation) will prove to be of considerable importance for Rita in her subsequent research work. On the one hand, the young scientist became acquainted with the method of cell counts and the analysis of variations in the number of nerve cells induced by experimental manipulations. On the other hand, she also became familiar with the study of the sensory ganglia of the spinal cord. Being located outside the spinal cord and well delimited anatomically, these structures are more suitable to quantitative studies than other parts of the central nervous system (as – for instance – the motor columns, studied by Hamburger, which are located inside the grey matter of the cord).

This choice, together with that of the sympathetic ganglia, would prove to be a fundamental resource in the research conducted by Rita in the home laboratory at the time of the war (and also later, in America, in Hamburger's laboratory). This was because the relatively low and constant number of nerve cells in each single ganglion (and other structural features) would allow for a clear-cut and quantitatively precise assessment of the effects induced by the experimental manipulations of the embryos.

*The results of Rita's and Levi's experiments in the “laboratory à la Robinson Crusoe”*

In all, the experiments, conducted by the two Italian scholars in Rita's home lab, led, in the period 1942-1945, to the publication of five different articles, three of which authored by both Rita and Levi, and two written in Rita's exclusive name (refs. 20-24). Due to the racial laws, all these articles appeared in “non-Italian” journals: three of them – dated respectively 1942 and 1943 and 1945 – were printed in the Belgian journal *Archives de Biologie*. The other two appeared in the scientific journal published by the Pontifical Academy of Sciences (in the *Acta* or in the *Commentationes* of the *Pontificia Academia Scientiarum*). This was possible on the basis of the fact that Vatican City was considered an extraterritorial state with respect to

fascist Italy (“the *Pontificia Academia Scientiarum* – as Rita wrote many years later – did not discriminate racially”: Levi-Montalcini, 1997, p. 3).

The second of the two texts that appeared in the *Commentationes*, written together by Rita and Levi, is the most complete as regards the study of the correlation problem stimulated by reading Hamburger’s article (ref. 22). It is dated 1944, although it corresponds to a communication presented to the Academy on February 21, 1943. In 1945, a subsequent article appeared in the *Archives de Biologie* of Liège, with a main title that is the exact French translation of the previous one, and in the exclusive name of Rita (ref. 24). However, this article was aimed at the analysis of another aspect of the correlation problem, substantially different from that addressed by Hamburger in 1934.

It is interesting to note that the article, which could be the first scientific text to come out of the work done in Rita’s home laboratory, did not directly concern the problem faced by Hamburger in his 1934 publication. This article appeared in the Vatican journal in 1942, exclusively on behalf of Rita, a circumstance that might suggest that the research work, on which it was based, had been carried out before Levi joined the domestic laboratory (ref. 20).

The topic addressed by Rita in this first work was that of the neurogenesis, in the chicken embryo, of the accessory nucleus of the abducens nerve (the sixth pair of the cranial nerves). The development of the cranial nerves was a indeed a theme already present in Levi’s school, and – in particular – it had been the subject in 1921 of a research by Tullio Terni, the first of Levi’s pupils. Analysing Rita’s bibliography in the early years of her career, up to the beginning of the American period, it is quite evident that the neurogenesis of the cranial nerves was the long-term research program she had planned for her work in the Anatomical Institute of Turin, in the period preceding the promulgation of the racial laws.

Before describing and discussing in detail the experiments on the “correlation” reported in the papers by Rita and Levi in the period 1942-1945, it is necessary to emphasize the truly “extraordinary” nature of the research activity of the two Italian scientists in this period. It was a time when most people – and Jews in particular – were almost uniquely absorbed by every

possible effort to save their lives in the face of dangers and immediate threats, while the whole world around them seemed to collapse. On their side, Rita and Levi were totally absorbed in scientific problems that probably seemed rather trivial to those around them (and perhaps sometimes to themselves).

Surprising was also the fact that in a condition in which any type of activity was difficult, and in particular the scientific one, the two scholars were able to carry out “at home” experiments that required a rather sophisticated apparatus. Their research needed also an effort of organization that was not exactly simple in those difficult periods. In particular, in conditions of great food shortage a not easy problem was that of obtaining the fertilized eggs necessary for the investigation. It is worth remembering here that in Bremer’s laboratory in Brussels, one of the best equipped physiology laboratories in the world, Rita had failed, because of trivial technical problems (as the malfunctioning of a thermostat), to keep her embryos alive. Now she was able to conduct a difficult research on these same preparations, in very difficult circumstances (truly comparable to those in which the legendary hero of Defoe had found himself on a remote and wild American island).

Another surprising element was that two scientists whose names clearly indicated their Jewish ancestry could publish articles in journals printed in Belgium during the Nazi occupation.

As already mentioned, unlike Hamburger and – before him – Shorey, who had studied mainly the motor columns of the spinal cord – in their research on neurogenesis in the chicken embryo published in the period 1942-1945, Rita and Levi focused their attention especially on the sensory spinal ganglia. In particular, they chose a particular ganglion, the one corresponding to the 25<sup>th</sup> segment (i.e. that in the centre of the group of segments responsible for the sensory innervation of the hind limb). As they pointed out, in particular in their 1944 article, this procedure was essential, because, in the case of spinal motor neurons, investigated by Hamburger and Shorey, it was impossible to study the modifications induced by experimental manipulations with a rigorous quantitative method. In the ganglia, on the other hand, it was easy to do this, for anatomical reasons (their anatom-

ical individuality and separation from the medulla), in particular if an adequate method of staining was used (such as the silver impregnation of Cajal-De Castro that Rita knew very well).

With this long-standing and glorious method it was possible to distinguish neurons, in the various stages of their differentiation, from undifferentiated cells and from supporting (or other non-nervous) elements. This was mainly because of selective staining of neurofibrils, which were not detected by the methods based on haematoxylin used by Hamburger and Shorey.

Another important problem and source of fundamental differences with the results of the two Italians was that Hamburger (and Shorey before him) had limited his study of the spinal cord to a very short, and rather late, period after the experimental ablation. Because of this, the previous authors could not detect the initial modifications induced by the extirpation of the peripheral tissue, modifications which – in the hands of Rita and Levi – proved to be of fundamental importance for clarifying the mechanisms underlying the embryonic development of the nervous system.

Some of the experiments of the two Italian scholars were also conducted on sympathetic ganglia. In addition to allowing, as we have said, a more rigorous study of the effects of experimental manoeuvres, these choices will prove, in retrospect, very fortunate, because the sensory and sympathetic ganglia of the spinal cord are the privileged target of NGF (then still to be discovered).

The main “discrepancy” with respect to previous studies, and in particular to that of Hamburger, which emerged from Rita’s and Levi’s researches concerned the initial effects induced by the ablation of peripheral structures on the development of nerve sketches. According to the conceptual framework to which Hamburger was referring, the ablation of the limb buds should have caused a lack or reduced development of the corresponding nervous structures, because the lack of a stimulus capable inducing the growth of the nerve centres responsible for their innervation. As mentioned Hamburger described his results as effects of reduced growth, or hypoplasia.

In their study Rita and Levi instead observed that, after the ablation of a peripheral structure (usually the bud of the hind limb of one side removed of

the third day of incubation – the bud of the other side being left normal for control), there was initially normal growth of the ganglion cells responsible for their innervation. Indeed, at the initial stages there no significant difference between the operated side the control side. In fact, there was therefore no evidence of the reduced proliferation that should have occurred in the absence of the hypothetical growth-inductive action of the peripheral tissue.

Only in the most advanced stages of embryonic development (starting from the sixth day of incubation, that is, three days after ablation), Rita and Levi observed a significant decrease of nervous elements. However, this phenomenon – far from being caused by a reduced development of the nerve centres – appeared to be the consequence of a profoundly different (and somewhat unexpected) process, hard to reconcile with the existing theories. It was the effect of a degeneration, in some way secondary, which involved nerve cells already adult and differentiated (that is, rich in neurofibrils, and which had already emitted the process intended to form the neurite – this was term used to designate the axon designated as “neurite” by Rita and Levi). These adult-type cells progressively lost their specific characters, while the undifferentiated nerve elements continued their proliferation and growth at a substantially normal rate. The phenomenon became more and more accentuated with the passing of days, to the point that in the advanced stages, the proportion of differentiated neurons compared to those without signs of differentiation (i.e. without fibrils and neurites) changed by about 20 percent between the injured side and the control side .

Based on their experiments Rita and Levi came to the following consideration:

During the first period, the development of the centres is not altered at all. Moreover, the reduction in the number and size of sensory neurons, differentiated with neurofibrils and provided with neurites, begins to occur only after that the neurites of these neurons have reached a certain length and cannot, due to the ablation of the bud, reach the peripheral organs for which they are intended (receptors of the skin of the muscles). It seems therefore probable that the dis-

appearance of a considerable number of neurons and the reduction in the size of other neurons (and also the atrophy of well-differentiated neurons) observed in our experiments can be explained by the absence of normal synapses at the level of peripheral neurites. (ref. 21, pp. 544-545).

In other words, after the peripheral ablation, the centres of the spinal cord that in the course of normal development are destined for their innervation (sensory or sympathetic ganglia) develop normally in an initial phase, as if they were not affected at all by the absence of the target organs. Only subsequently do they undergo a phenomenon of degeneration. The presence and regular development of the peripheral target structures operate apparently in such a way as to maintain the normal condition of the fully mature cells, preventing, in the late phase of embryonic growth, their degeneration. That is, they do not work, as supposed by the previous authors – and in particular Hamburger – by producing, in the initial phases, an inductive stimulus factor necessary to favour their multiplication and differentiation.

In the résumé of their article, the two Italian scientists summarize their results by saying that “from the count of less differentiated [nerve] cells, carried out both on the control side and on the operated one, it appears that, in all stages, the number is approximately the same on both sides”. Against the interpretation of previous authors (Shorey and Hamburger) they conclude with this rather peremptory statement: “the hypothesis advanced, according to which cell multiplication is regulated by the peripheral field, has not been supported by our research”. (*ibidem*, p. 545)

The article in extenso of 1944, published in the Vatican *Commentationes* was based on a large number of experiments, each of which involved the counting of a number of nerve cells varying between 500 and 1000 elements, and the measurement of their size. It came again old Levi’s obsession with counting and measuring, performed at various stages of development and with a rigorous chronological sequence (which usually caused the bad mood of internal students and collaborators). Furthermore, the results were summarized and illustrated with extensive use of tables and graphs, this also being a characteristic of Levi from his early years.

The conclusions of the 1942 work were

strengthened and clarified, based on an experimental effort that would have appeared “heroic” in any circumstance, but which was even more impressive due to the decidedly exceptional conditions in which it was performed (a home laboratory, operated by two Jewish scholars, at the time of the racial persecutions):

Only the differentiated neurons in which neurofibrils have formed and neurites have appeared, regress due to the lack of the limb; the regression begins 70 hours after the operation, thus coinciding exactly with the moment in which the neurites, if development had proceeded undisturbed, would have reached the terminal organs of the limb. (ref. 23, p. 556).

Rita and Levi summarized their interpretation with this statement:

The absence of the limb therefore does not inhibit the multiplication of undifferentiated cells, nor the specific differentiation of these into neurons, both in early and later periods; the tendency to differentiate is a property inherent in the elements of the nervous centres, because it is transmitted to them in a hereditary way. On the other hand, when the neurites of neuroblasts grown in length are unable to grow further and to make normal connections with the peripheral elements of the teguments and muscles, the regressive process begins both in the pyrenophore [i.e. the cell body] and in the neurites. (*ibidem*, p. 558)

As mentioned, the conclusion of the two papers by Rita and Levi represents what could be considered a real paradigm shift in the history of neuroembryology. From an inductive paradigm, in which the peripheral tissue (to be innervated), induces the proliferation of precursors of nerve cells and stimulates their differentiation, we pass to a paradigm of a different type, based on the idea of growth of nerve centres independent of their target peripheral organs. The intervention of an action originating from peripheral structures would occur only at a later stage, and would serve to maintain the condition of mature nerve cells, already grown, preventing their degeneration.

The idea of an embryonic development that implied, during its normal course, a mechanism of de-



generation - in some way programmed - was definitely outside the conceptual schemes of the time. Growth was seen as the fundamental expression of life, and the phenomena of degeneration and loss of living substance were considered only accidental and random processes. The idea that nerve cells were somehow programmed to die, even before the death of the organism, and that they were preserved from this “physiological” death through the action of peripheral structures, was certainly a great biological novelty. It contained – albeit in the background and in a still unclear way – a truly revolutionary principle that anticipated the times, and which will be fully understood many years later with the studies on apoptosis, or programmed cell death.

It should be noted here that, in both in the 1942 and in the 1944 article, in interpreting their results, Rita and Levi excluded any intervention of chemical factors (of the type supposed by Shorey). In their idea, to be responsible for the late degeneration of differentiated neurons would instead be “the impossibility of growing further and contracting normal connections with peripheral elements”. This “connectivistic” conception was more in line with what Rita had glimpsed in her research a few years earlier together with Visintini. As we have already said, the two young scholars had observed that some terminations of the vestibular fibres, unable to form normal synapses, underwent degenerative phenomena that resembled the *bolae* observed many years earlier by Cajal in different circumstances, but always in relation to degenerative phenomena (see ref. 1).

In a narrative of the beginnings of her research published in 1997 Rita writes that it was she who actually supported the hypothesis “that the inability of sensory neurons to establish synaptic contacts with their target organs was responsible for the massive death of these cells” (ref. 25, p. 3).

The idea of a chemical factor (as anticipated by Shorey in 1909) will surface later in Rita’s research. This would occur during the first period of her work together with Hamburger in St. Louis. A long time would be necessary, however, to assert it with certainty. Some crucial experiments performed by the Italian scientist in America, together with her collaborators, and in particular Stanley Cohen, will show beyond any doubt that is indeed a diffusible chemical agent

the factor responsible for the preventive effect of neuronal degeneration, exerted by peripheral tissues on the development of the nerve centres. This agent, which will be shown to be also produced by structures very different of the embryonic limb buds (including some tumours, the venom organs of some snakes, and the salivary glands of some animals), was eventually identified by Rita and Stanley Cohen and finally named Nerve Growth Factor (NGF, as we know). Synthesized in the course of development by some peripheral tissues waiting to be innervated, the NGF is transported in a retrograde way to the cell body where it acts through a complex series of chemical events whose identification has marked the opening of an entirely new field of modern biology (refs. 5, 25 and 27).

*The mysteries of the letter from America, and the a posteriori narration.*

As repeatedly mentioned, due to a series of complex and rather fortuitous circumstances, the experimental differences between the results obtained in the home laboratory and those reported in the 1934 Hamburger’s paper ended up constituting one of the most important turning points in Rita’s scientific career. This happened in particular because these articles came to the attention of Hamburger, arousing his keen interest in the results reported by the two Italian scholars, to the point of inducing him to invite Rita to America, in order to continue his research in his laboratory in St. Louis.

According to Rita’s recollections, Hamburger had the opportunity to read both the short article published (in 1942) in the Belgian *Archives de Biologie*, and the paper in extenso appeared (in 1944) in the Vatican journal (written respectively in French and Italian, the second with an abstract in Latin, both in the name of Rita and Levi) (see ref. 25, p. 3). Neither periodical was (nor is it at the time this article is written) in the library of Washington University. From the letter Hamburger sent to Levi on July 8<sup>th</sup>, 1946, we learn that he received the article through the Italian ambassador in Washington (probably some embassy official informed Hamburger that Levi had returned to his Turin Institute at the end of the most dramatic phase of the war).

In the Hamburger’s letter (originally written in German, but translated by himself into English at a

much later date), the German-American scientist mentions his own initial and unsuccessful attempts to reach Levi. He writes that the previous year (namely in 1945) he had sent a letter with the reprints of some of his publications to an address in Florence indicated by “Dr. Luria” (i.e., Salvador Luria, that is Rita’s colleague emigrated – as we know – to America in 1940 as a result of the racial laws), but – he adds – “everything was returned to me as undeliverable”.

In the 1946 letter, Hamburger does not specify how many and which articles published in previous years by Levi and Levi-Montalcini he had received, but it is likely that he received them all. This is because, in discussing the concordances and discordances between his own experiments and those of the Italian colleagues, he cites an experiment involving a brain stem lesion which is reported and discussed in the last article of the series, namely the one published in 1945 in the Belgian magazine, in the exclusive name of Rita.

In a conference on Giuseppe Levi held in Turin in May 2019, one of Rita’s pupils, Antonino Cattaneo, has pointed the attention on a rather intriguing aspect of the 1946 letter to Levi.<sup>2</sup> This is the passage where Hamburger insists on the fact that, because of the time required to verify their respective results, Rita should stay in his laboratory for at least one year or two. This contrasts with most of Rita’s memories in which the scientist says she was invited for a period of six months. Only in a few circumstances, Rita speaks of a longer period (one year), and in a video recording produced in 2000 he even said that she was “invited for three months” (see ref. 28).

Life events would “dramatically” change this initial perspective on length of stay in the United States, and Rita would spend many years of her long life in America, working in the Department of Zoology at Washington University in St. Louis. For about 25 years, she will stay there without interruption, and then, until the 1980s, she will spend half the year in St. Louis and half in Rome, where she was initially granted a laboratory, by the *Istituto Superiore di Sanità* (ref. 27).

Alluding to a considerably shorter period, Rita

was probably transposing to the contents of Hamburger’s letter what at the time was her idea of the length of her stay abroad; and also the wishes of her family, who – as we know – even in earlier occasions, was averse to a long separation from the young woman.

A clue as to the reasons for Rita’s distorted memory comes from the consideration that at that time there was a strong sentimental interest in her on the part of a classmate, Guido. Guido was the friend who – as she narrates in the *Elogio* – used to walk with her along the avenues of the Valentino Park of Turin, and drove her on motorbike to the hills around the town (he was the same Guido in the episode of the reading of Hamburger’s 1934 paper).

When Rita was invited by Viktor Hamburger to



**Figure 11.** Rita Levi-Montalcini in a photo of 1948, at the gardens of the Marine Biological Laboratory of Woods Hole (© Piera Levi-Montalcini).

2 - The video of this presentation is available at this address: <https://www.youtube.com/watch?v=2N8Wz9Wdxdk>

go to St. Louis to conduct experiments on the development of the nervous system, the friendship with Guido (seen with some suspicion by the girl's family especially for the swaggering nature of the young suitor), imposed a choice on Rita. According to a version of which there are traces in family memories, the departure should serve to verify – with the programmed separation of some months – the strength and seriousness of the love bond between the two young people. Hamburger refers to a slightly different version, but always based on the existence of a suitor, in a private manuscript written in May 1989, entitled “The Queen and I”. In the first part of this text, which bears the subtitle “Rita - Enigma?”, Hamburger writes, undoubtedly based on what Rita herself had said: “one of the reasons for her avid acceptance of my invitation to come to St. Louis in 1946 was to escape from a suitor”.

Whatever it is, probably the relation with Guido was, for one reason or another, one of the factors that pushed Rita, generally reluctant to leave her family, to face the scientific emigration journey to the new continent in 1947. By saying that she had been invited for a period of six months (or even less), probably she was transposing to her recollections what was - at the time - idea about the length of the staying in St. Louis (and not the actual one-two years period indicated as necessary by Hamburger).

This distorted recollection by Rita on the prospective duration of her America sojourn might appear of relatively trivial importance. Certainly more relevant is the fact that, in all probability, the research conducted with Levi in the legendary home laboratory became truly fundamental for Rita (and such as to condition her entire scientific career and her life) only in retrospect, and only because of the extraordinary developments of the St. Louis period.

Let's try to see what clues exist to support this hypothesis.

If Rita and Levi had immediately sensed the revolutionary aspect of their discoveries in the war period, there would be little doubt that, at the time of the resumption of the ordinary experimental activity in the Anatomical Institute, they would have promptly dedicated themselves to the continuation of this type

of research. Especially Rita, a young scientist and certainly less burdened by the commitments that certainly lay over Levi, who was then reorganizing the research activity in his Institute and resuming the teaching activity in the Faculty of Medicine.

This did not happen. In the after-war period, the publications of Rita (who had found an institutional collocation in the “Study Center on the growth and senescence of organisms” newly created in Turin, on the initiative of Levi, by the Italian National Research Council) were all dedicated to the study of the development of the cranial nerves. As said, this was a traditional line of research of Levi's group, to which Rita had devoted herself in the last period she spent in the Anatomical Institute in the pre-war period. It had also been – as we have noted above – the subject of the first research performed in 1940 in the home laboratory, and the argument of her first publication appeared in 1942 in the Vatican *Acta*.

In the period 1946-1947 Rita in fact published seven scientific articles (mostly short notes presented by Levi at the *Accademia dei Lincei*, but also an article in extenso, in collaboration with Amprino, in the Belgian *Archives de Biologie*: see refs. 29-34). Six of them were dedicated to the origin and development of the cranial nerves, and one concerned the sympathetic thoraco-lumbar system. Although in one of these researches Rita intervenes in the embryo with the removal of the mesencephalic vesicle, none of these articles clearly takes up the themes that had been the focus of research in the home laboratory during the war period.

Even the first article of the St. Louis period, which appeared in 1949 and was signed solely by her, Rita focuses on the theme of cranial nerves. It concerned the development of the acoustic-vestibular system and was a direct continuation of the research on the auditory system carried out in Turin, in the immediately post-war period (ref. 35) . However, this article also addresses the “theme of correlation”, which Rita had begun to study in the home laboratory, and which will then be at the centre of her research with Hamburger, marking the resumption of the journey of the NGF. It is no coincidence, however, that, in this 1949 article, Rita appears with the double affiliation, as a member of both the Turin Institute of Anatomy and the American Department of Zoology, a fairly probable indic-

ation that part of the research was done in Turin. This idea is supported by a passage from the second part of the private Memorandum, written in manuscript form by Hamburger in 1989, with the subtitle: “The Years of Collaborations (1947-1953)”:

Hamburger writes about Rita:

She brought with her the microscope sections of a large amount of material of early embryonic otocyst extirpation in which the effects of the operation on the cochlear and vestibular centers were to be studied. I suppose she had studied this material already, but I don't remember if she brought with her protocols, notes or pictures. At any rate, not being familiar with neurology, I had to learn all about the nucleus angularis, magnocellularis, laminaris, etc., and I worked extensively with her on the slides (Hamburger, 1989, p. 12)

With reference to the last sentence of this quo-



**Figure 12.** Viktor Hamburger and Rita Levi-Montalcini in their mature age (© Piera Levi-Montalcini).

tation, it is interesting to note here *en passant* that, as it had occurred with Levi in the home laboratory, also in this case Rita acted as the chief investigator, with a famous scholar as her assistant.

All this outlines a substantial picture of continuity between the research conducted by Rita between the period immediately preceding and that following the war. We are thus induced to suppose that at the time she did not perceive the revolutionary scope of the research in her laboratory “à la Robinson Crusoe”, and all became truly revolutionary, and epic as well, only in retrospect, after the NGF discovery.

To what should we attribute this? To a scarce insight of Rita?

Difficult to think of such a thing for a person of Rita's intelligence and astuteness, able (as often she says, even in private letters) as few to understand the importance of the results, and to identify the directions in which to pursue her research, endowed as she was with a special flair for the big scientific “truffles” (see ref. 2).

In fact, in themselves, the experiments with Levi during the war period, although undoubtedly stimulating and useful in demonstrating the groundlessness of some previous hypotheses on the mechanisms of embryonic development of the nervous centres, were revolutionary only *a posteriori*, on the basis of evolutions then difficult to foresee.

Apparently in contrast to what previously said, they could, instead, be “accommodated” within the context of relatively consolidated scientific concepts, on the basis of certain considerations. At the time, it was well known that, even in the case of humans, congenital atrophy of a limb often involved a reduced development of the motor centres responsible for its innervation. Also known was that even the simple physiological inactivity could involve – on both on the motor and sensory fields – a more or less marked atrophy of the corresponding nervous structures. On those grounds, it should not therefore appear so surprising that there was a degeneration of the nerve fibres and cells after ablation of the corresponding peripheral structures. This is because, following the extirpation of the limb, both the correct anatomical relationship between nerve fibres and peripheral tissues to be innervated (on both

the sensory or motor side) were missing, and – consequently – the functional stimulus acting on the nerve cells was reduced or abolished. This was a particularly easy possibility to suppose for Rita and Levi, because of their supposition that the element responsible for nervous trophism was, not so a chemical agent released from peripheral tissues, but a correct synaptic relationship between the nerve fibres and their targets.

The perspective will totally change, when the chemical nature of the trophic agent involved in these experiments becomes clear. This will happen especially with the “casual” discovery of some mice with a particular type of tumour capable of inducing effects similar to those of the mysterious peripheral agent; and with the experiments conducted with explants of this tumour on cultured cells. And then with the demonstration that the injection of a tumour extract into the allantoic cavity of the embryo was able to produce an extraordinary growth of cells and nerve fibres throughout the organism, in the absence of any direct contact between tumour cells and tissues peripheral. A result that, among other things, also excluded the viral nature of the agent (taken into consideration at a certain point), and brought materials to support its physiological action during normal development. And finally, along this line, the “immuno-sympathectomy” experiments, that is, the suppression of the growth of the sympathetic system induced by the administration of antibodies against the agent yet to be identified in its precise chemical structure (see refs. 26 and 28).

All this was contained *in nuce* in the results obtained in the small home laboratory, by the young scientist and the elderly teacher, but not even a very perspicacious “truffle dog” like Rita could then understand the extraordinary significance that those results contained in perspective.

What will happen next, in the St. Louis period, will also change the memory of all this, and will give this extraordinary woman, also gifted with considerable literary talent, the opportunity to narrate with vivacity and charm things that could have been lost in the river of forgotten memory. As the article read on the cattle cars train slowly advancing in the Turin countryside, on a rather ordinary day, destined years later to be remembered as fateful.

History, as we know, is how it is told. For this

reason, in order to have a proper and wider perspective of the events that have really taken place, those events should be narrated and discussed not exclusively by those who have experienced it first-hand.

This is what I have endeavoured to do in this article.

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# Rita Levi-Montalcini's first intellectual emigration and her research in the laboratory "à la Robinson Crusoe": the letters from Brussels and a "Wiggish" recollection

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**Abstract.** This article deals with the first part of the research eventually leading Rita Levi-Montalcini to her discovery of the Nerve Growth Factor (NGF), and particularly with the experiments carried out, in collaboration with her mentor, Giuseppe Levi, during the last world war period, in the laboratory as "à la Robinson Crusoe" that she had set up at her home in Turin. In her various recollections of the NGF discovery path, Rita regarded those experiments as an heroic and revolutionary research period of her scientific life. Nevertheless, at the time they did not appear to her innovative enough such to change immediately the ordinary research program she was pursuing in the pre-war period. We argue that Rita's narration of her initial experiments reflects a somewhat Wiggish attitude, and we discuss the possible reasons underlying her stance.

**Keywords.** Rita Levi-Montalcini, History of neurosciences, Giuseppe Levi, neuroembryology, Nerve-Growth-Factor, wiggish.

## La prima emigrazione intellettuale di Rita Levi-Montalcini e gli esperimenti nel "laboratorio alla Robinson Crusoe": Le lettere da Bruxelles e una ricostruzione di tipo "Whiggish"

**Riassunto.** Questo articolo tratta della prima parte della ricerca che ha portato Rita Levi-Montalcini alla scoperta del Nerve Growth Factor (NGF), e in particolare degli esperimenti condotti, in collaborazione con il suo mentore, Giuseppe Levi, durante l'ultima guerra mondiale, nel laboratorio "alla Robinson Crusoe" da lei allestito nella sua casa di Torino. Nelle sue varie ricostruzioni del percorso di scoperta dell'NGF, Rita considerava quegli esperimenti come un fase particolarmente eroica e rivoluzionaria della sua vita scientifica. Tuttavia, all'epoca in cui furono condotti, i risultati ottenuti non le apparvero talmente innovativi da indurla a mutare immediatamente il programma di ricerca ordinario che stava portando avanti nel periodo prebellico. Nella nostra opinione la narrazione che Rita fa dei suoi esperimenti iniziali riflette un atteggiamento *a posteriori* (di tipo in parte "Wiggish") di cui cerchiamo di analizzare qui le possibili ragioni.

**Parole chiave.** Rita Levi-Montalcini, Storia delle neuroscienze, Giuseppe Levi, neuroembriologia, Nerve-Growth-Factor, storia "whiggish".

## La primera emigración intelectual de Rita Levi-Montalcini y los experimentos en el "laboratorio alla Robinson Crusoe": Las cartas de Bruselas y una reconstrucción de tipo "Whiggish"

**Resumen.** Este artículo trata de la primera parte de la investigación que llevó a Rita Levi-Montalcini al descubrimiento del Factor de Crecimiento Nervioso (NGF). En particular, se abordan los experimentos realizados - en colaboración con su mentor, Giuseppe Levi - durante la última guerra mundial, en el laboratorio "à la Robinson Crusoe" que ella instaló en su casa en Turín. En sus diversos recuerdos del proceso de descubrimiento de NGF, Rita considera esos experimentos como una fase particularmente heroica y revolucionaria

# How vary the Mindfulness Skills Before and During COVID-19 pandemic among Italian nurses: a retrospective cohort observational study

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**Abstract:** This study identified and quantified the Mindfulness skills “Before” and “During” the Covid-19 pandemic. Data were in agreement to the current literature: the implementation of techniques aimed at increasing Mindfulness skills in clinical nursing practice has an effective a cost-benefit ratio all to the advantage of health company than professionals.

**Keywords:** Mindfulness; Nursing Personnel; Pandemic.

**Riassunto.** Il presente studio ha identificato e quantificato le abilità di Mindfulness “Prima” e “Durante” la pandemia di Covid-19. I dati risultano essere concordi con la letteratura corrente: l’implementazione di tecniche volte ad aumentare le competenze di Mindfulness nella pratica clinica infermieristica ha un effettivo rapporto costi-benefici a tutto vantaggio dell’azienda sanitaria rispetto ai professionisti.

**Parole chiave:** Mindfulness; Personale Infermieristico; Pandemia.

**Resumen.** Este estudio identificó y cuantificó las habilidades de Mindfulness “antes” y “durante” la pandemia de Covid-19. Los datos coincidieron con la literatura actual: la implementación de técnicas orientadas a incrementar las habilidades de Mindfulness en la práctica clínica de enfermería tiene una relación costo-beneficio efectiva todo en beneficio de la empresa de salud que de los profesionales.

**Palabras llave:** Mindfulness; Personal de enfermería; Pandemia.



## Introduction

The Covid-19 pandemic has rapidly invaded the world's territory causing a health emergency condition unprecedented in the last century (1). This condition has strongly influenced the lives of all individuals (2), in particular that of health professionals (3), who are entrusted with the direct care of patients affected by SARS-CoV-2 infection.

Unfortunately, the high contagiousness of the virus places further stress on healthcare professionals, in particular nurses assigned to direct care of COVID-19 patients. There are now numerous studies in the literature focused on the psychological state of nurses and on the psychological support interventions to be made to allow nurses to work with a serene and fearless psychological state (4-6).

In this regard, numerous scientific evidences come from the literature that exalt the intervention of Mindfulness as an indispensable support to protect nurses and other health professionals from the pressing psychological condition dictated by the COVID-19 pandemic (7-9).

Particularly, Mindfulness alludes to the recognition of the present instant and agreeing of introspections and emotions without judgment (10). Literature evidences that Mindfulness is correlated with an approach of reception (11). Thus, persons who possess high Mindfulness skills are able to cope better with situations and to incur less in conditions of psychological distress. This is why the literature is full of references on the importance of implementing mindfulness programs, particularly among nurses where it is easy to incorporate the stress and fatigue of daily work and this technique could undoubtedly reduce occupational stress (12).

The purpose of the present study is to identify and quantify the Mindfulness skills "Before" and "During" the Covid-19 pandemic, underling the existence of some differences among data collected. Specifically, this study purposed the following question: are there any differences in the Mindfulness skills assessment between "Before" and "During" the Covid-19 pandemic?

## Materials and Methods

### *Strategy approach*

The questionnaire was administered on line through the Google Moduli application and was spread to some on-line nursing group pages from May 2020 to June 2020 in order to interview nurses who were engaged in the first line to care patients suffered from the Covid-19 with the aim to better understand if this particularly health worldwide emergency have influenced the Mindfulness skills among nurses. Particularly nurses were invited to answer relating the period "Before" the pandemic (from November 2019 to January 2020) and then concerning the period "During" the pandemic (from February 2020 to April 2020).

### *The Questionnaire*

An on-line questionnaire was created to study if nursing Mindfulness skills changed during the health emergency due to the Covid-19 pandemic.

In the first part of the questionnaire administered a series of general information was collected, as: gender, age group (divided into four different classes, namely: 20-30 years, 31-40 years, 41-50 years, 51-60 years) and the Region of Italy where nurses work, as: North of Italy, Centre, and South of Italy.

Subsequently, in the second part of the questionnaire, the Kentucky Inventory of Mindfulness Skills (KIMS) was administered to assess four dimensions of the Mindfulness skills, generally focused one's attention in a non-judgmental or accepting the experience occurring in the present moment<sup>13</sup>.

The 39-items of KIMS aimed to assess four Mindfulness skills' dimensions, specifically:

- "Observing": Mindfulness includes observing to different encouragements involving internal and external factors, such as: body perceptions or sounds and smells. For this dimension it includes items number: 1,5,9,13,17,21,25,29,30,37,39.
- "Describing": Mindfulness assessment embraces interviewer detailing or perceived happening by employing words in a non-estimated approach. For this dimension it includes items number: 2,6,10,14,18,22,26,34.
- "Acting with Awareness": Mindfulness includes full

participation in one's activity. Items included for this dimension are: 7,11,15,19,23,27,31,35,38.

- "Accepting (or allowing) without judgment": Mindfulness involves to live the reality without or avoiding prejudice. Items included are: 4,8,12,16,20,24,28,32,36.

For each items a 5-point Likert scale was associated ranging from 1(never or very rarely true) to 5 (almost always or always true). High scores stated for more Mindfulness.

#### *Ethical consideration*

Participation was voluntary and no form of personal restitution of the results obtained was involved.

All the information collected were treated confidentially, guaranteeing complete anonymity. The participation to the on-line questionnaire was an implicit consent. All nurses who agreed to participate in the survey returned the questionnaire, while those who disagreed did not return it.

This study was approved with id number 6161 by the Community Review Board (CRB) of General Hospital, Policlinic of Bari, Italy.

#### *Validity and Reliability*

In this study it was adopted a homogenous instrument to assess Mindfulness skills levels among Italian nurses, which contained 39 items that well measure skills' levels and its consistency among responses of multiple users was validated from other studies (13).

#### *Data analysis*

Collected data were entered in an Excel sheet and statistical processing was performed with the IBM SPSS program version 20.

Socio-demographic information of the Italian nursing population was presented as frequencies and percentages for categorical variables, while differences existing according to the two periods considered, as "Before" and "During" the pandemic were sowed as means  $\pm$  standard deviations and differences among them were assessed thanks to the t-test for paired samples. Data obtained  $<0.05$  were considered as statistically significant.

## Results

In total, 104 nurses answered the questionnaire. Of these, 65.4% were women and 34.6% were men (Table 1). 44.2% were aged between 20-30, 13.5% were aged between 31-40, 18.3% were aged between 41-50, 24% were aged between 51-60 years. 57.7% of nurses worked in a Region of the Southern of Italy, 26.9% in a Region of the Northern of Italy, 15.4% of nurses worked in a Region of the Central of Italy.

Tables 2-5 show the data collected by administering the KIMS questionnaire, dividing the items already by dimension of the Mindfulness.

Specifically, Table 2 shows the results obtained for the "Observation" dimension, Table 3 illustrates the results concerning the "Describing" area, Table 4 highlights the results obtained by investigating the "Act with Awareness" dimension and, finally, Table 5 shows the results obtained regarding the "Accept without judgment" dimension, all Tables consider both "Before" and "During" periods of the Covid-19 pandemic.

As shown in Table 2, in almost all the items considered there is a variation, either increasing or decreasing, statistically significant, with the exception of items no. 9 ( $p=0.511$ ), no.30 ( $p=0.262$ ), no.33 ( $p=0.396$ ). As regards items no. 5, 13, 17, 21, 37, 39, data show a significant increase of the Mindfulness skills in the period "During" the pandemic ( $p<0.001$ ,  $p<0.001$ ,  $p<0.001$ ,  $p<0.001$ ,  $p<0.001$ ,  $p=0.041$ , respectively). Instead, a statistically significant decreasing is recorded for items no. 1, 25, 29 ( $p <0.001$ ,  $p <0.001$ ,  $p <0.001$ , respectively) in the "During" Covid-19 period.

**Table 1.** Sampling characteristics (n=104).

Variables	Frequencies (n)	Percentages (%)
<b>Sex:</b>		
Female	68	65.4
Male	36	34.6
<b>Age:</b>		
20-30 years	46	44.2
31-40 years	14	13.5
41-50 years	19	18.3
51-60 years	25	24
<b>Region of belonging:</b>		
North of Italy	28	26.9
Centre of Italy	16	15.4
South of Italy	60	57.7

**Table 2.** “Observe” factors of the Kentucky Inventory of Mindfulness Skills in a Nursing Sample (n=104) “Before” and “During” the COVID-19 pandemic.

Item Number and Content	Before COVID-19	During COVID-19	p value
	Means $\pm$ SD	Means $\pm$ SD	
1. I notice changes in my body, such as whether my breathing slows down or speeds up.	4.22 $\pm$ 0.95	3.16 $\pm$ 1.11	<0.001*
5. I pay attention to whether my muscles are tense or relaxed.	2.71 $\pm$ 1.13	3.35 $\pm$ 1.09	<0.001*
9. When I'm walking, I deliberately notice the sensations of my body moving.	2.67 $\pm$ 1.12	2.76 $\pm$ 1.06	0.511
13. When I take a shower or a bath, I stay alert to the sensations of water on my body.	2.25 $\pm$ 1.08	2.78 $\pm$ 0.98	<0.001*
17. I notice how foods and drinks affect my thoughts, bodily sensations, and emotions.	2.58 $\pm$ 1.01	3.36 $\pm$ 1.11	<0.001*
21. I pay attention to sensations, such as the wind in my hair or sun on my face.	3.07 $\pm$ 1.05	3.73 $\pm$ 1.06	<0.001*
25. I pay attention to sounds, such as clocks ticking, birds chirping, or cars passing.	3.64 $\pm$ 0.86	2.83 $\pm$ 1.03	<0.001*
29. I notice the smells and aromas of things.	3.10 $\pm$ 0.93	2.58 $\pm$ 1.05	<0.001*
30. I intentionally stay aware of my feelings.	3.59 $\pm$ 1.04	3.73 $\pm$ 1.06	0.262
33. I notice visual elements in art or nature, such as colors, shapes, textures, or patterns of light and shadow.	2.58 $\pm$ 1.01	2.69 $\pm$ 1.14	0.396
37. I pay attention to how my emotions affect my thoughts and behavior.	2.51 $\pm$ 1.07	2.87 $\pm$ 1.14	0.009*
39. I notice when my moods begin to change.	3.10 $\pm$ 0.93	3.36 $\pm$ 1.11	0.041*

\*p<0.05 is statistically significant.

Table 3 shows the “Describing” factors of the KIMS questionnaire. Particularly, for items no. 2, 6, 14, 18, 34 there is no statistically significant difference (p=0.078, p=0.175, p=0.102, p=0.798, p=0.403, respectively). Only for item no. 10 there is a statistically significant increase in the “During” Covid-19 period (p=0.020). While for items no. 22 and 26 there is a decrease in the value recorded in the period “During” Covid-19 (p<0.001, p<0.001, respectively) for all the two items considered.

Table 4 shows the values of the KIMS as regards the “Act with Awareness” dimension. Only the item no. 11 shows no statistically significant difference between “Before” and “During” Covid-19 period (p=0.462). On the other hand, there is a statistically significant increase in the “During” Covid-19 period for items no. 3 (p=0.026), no.15 (p<0.001), no.19 (p<0.001), no.23 (p<0.001), no. 27 (p<0.001), no. 35 (p<0.001). On the other hand, there is a statistically significant decrease in the “During” Covid-19 period for items no.7 (p<0.001), no. 31 (p<0.001), no. 35 (p<0.001), no. 38 (p=0.016).

Finally, Table 5 shows the KIMS values concerning the “Accept without Judgment” between “Before” and “During” the Covid-19 period. Only for the item no.32 there is no statistically significant difference (p=0.292). On the other hand, there is a significant increase in the values recorded for items no. 8 (p<0.001), no.12 (p=0.003), no.16 (p=0.017), no.20 (p<0.001), no.24 (p<0.001). Instead, there is a statistically significant reduction between the two periods for items no.4, no.28, no.36 (p<0.001, p<0.001, p<0.001, respectively).

## Discussion

The purpose of the present study was to quantify Mindfulness-related nursing skills and how these varied considering the Covid-19 health emergency as a determining event.

In the literature there are now numerous references to how the pandemic condition of Covid-19 has strongly influenced the lives of all people and, in

**Table 3.** “Describe” factors of the Kentucky Inventory of Mindfulness Skills in a Nursing Sample (n=104) Before and During the COVID-19 pandemic.

Item Number and Content	Before COVID-19	During COVID-19	p value
	Means $\pm$ SD	Means $\pm$ SD	
2. I'm good at finding the words to describe my feelings.	3.10 $\pm$ 1.14	2.85 $\pm$ 0.97	0.078
6. I can easily put my beliefs, opinions, and expectations into words.	3.30 $\pm$ 1.09	3.48 $\pm$ 1.04	0.175
10. I'm good at thinking of words to express my perceptions, such as how things taste, smell, or sound.	2.95 $\pm$ 1.30	3.36 $\pm$ 1.10	0.020*
14. It's hard for me to find the words to describe what I'm thinking <sup>a</sup> .	3.06 $\pm$ 1.16	2.82 $\pm$ 1.12	0.102
18. I have trouble thinking of the right words to express how I feel about things <sup>a</sup> .	3.06 $\pm$ 1.09	3.02 $\pm$ 1.03	0.798
22. When I have a sensation in my body, it's difficult for me to describe it because I can't find the right words <sup>a</sup> .	3.24 $\pm$ 1.03	2.30 $\pm$ 0.96	<0.001*
26. Even when I'm feeling terribly upset, I can find a way to put it into words.	3.64 $\pm$ 0.89	3.08 $\pm$ 1.06	<0.001*
34. My natural tendency is to put my experiences into words.	2.94 $\pm$ 1.09	2.83 $\pm$ 1.03	0.403

\*p<0.05 is statistically significant. <sup>a</sup> Reverse-scored item.

**Table 4.** “Act with Awareness” factors of the Kentucky Inventory of Mindfulness Skills in a Nursing Sample (n=104) Before and During the COVID-19 pandemic.

Item Number and Content	Before COVID-19	During COVID-19	p value
	Means $\pm$ SD	Means $\pm$ SD	
3. When I do things, my mind wanders off and I'm easily distracted <sup>a</sup> .	2.76 $\pm$ 1.00	3.10 $\pm$ 1.16	0.026*
7. When I'm doing something, I'm only focused on what I'm doing, nothing else.	3.57 $\pm$ 1.05	2.73 $\pm$ 1.08	<0.001*
11. I drive on “automatic pilot” without paying attention to what I'm doing <sup>a</sup> .	3.58 $\pm$ 1.10	3.47 $\pm$ 1.13	0.462
15. When I'm reading, I focus all my attention on what I'm reading.	2.33 $\pm$ 1.08	2.88 $\pm$ 1.14	<0.001*
19. When I do things, I get totally wrapped up in them and don't think about anything else.	2.70 $\pm$ 1.03	3.05 $\pm$ 0.97	<0.001*
23. I don't pay attention to what I'm doing because I'm daydreaming, worrying, or otherwise distracted <sup>a</sup> .	2.47 $\pm$ 1.06	3.42 $\pm$ 1.10	<0.001*
27. When I'm doing chores, such as cleaning or laundry, I tend to daydream or think of other things <sup>a</sup> .	2.51 $\pm$ 1.07	3.68 $\pm$ 1.05	<0.001*
31. I tend to do several things at once rather than focusing on one thing at a time <sup>a</sup> .	3.74 $\pm$ 1.10	2.30 $\pm$ 0.96	<0.001*
35. When I'm working on something, part of my mind is occupied with other topics, such as what I'll be doing later, or things I'd rather be doing <sup>a</sup> .	2.19 $\pm$ 0.91	2.92 $\pm$ 1.03	<0.001*
38. I get completely absorbed in what I'm doing, so that all my attention is focused on it.	2.71 $\pm$ 0.94	2.50 $\pm$ 1.01	0.016*

\*p<0.05 is statistically significant. <sup>a</sup> Reverse-scored item.

particular, that of health professionals, including the nursing class (4-6).

In general, the reported results show statistically significant evidence between the two periods of all 4 dimensions investigating KIMS. However, the results

report both significant increase in the “During” period and both significant decrease. Considering that the literature reports Mindfulness as an ideal approach for the psycho-physical and social well-being of man and, in particular in the period of health emergency, this

**Table 5.** “Accept Without Judgment” factors of the Kentucky Inventory of Mindfulness Skills in a Nursing Sample (n=104) Before and During the COVID-19 pandemic.

Item Number and Content	Before COVID-19	During COVID-19	p value
4. I criticize myself for having irrational or inappropriate emotions <sup>a</sup> .	3.28±1.07	2.27±1.00	<0.001*
8. I tend to evaluate whether my perceptions are right or wrong <sup>a</sup> .	2.43±1.02	2.97±1.26	<0.001*
12. I tell myself that I shouldn't be feeling the way I'm feeling <sup>a</sup> .	2.41±1.04	2.89±1.22	0.003*
16. I believe some of my thoughts are abnormal or bad and I shouldn't think that way <sup>a</sup> .	3.19±1.16	3.51±1.03	0.017*
20. I make judgments about whether my thoughts are good or bad <sup>a</sup> .	2.57±0.93	3.42±1.05	<0.001*
24. I tend to make judgments about how worthwhile or worthless my experiences are <sup>a</sup> .	2.31±1.04	3.31±1.14	<0.001*
28. I tell myself that I shouldn't be thinking the way I'm thinking <sup>a</sup> .	3.29±0.94	2.95±0.97	0.001*
32. I think some of my emotions are bad or inappropriate and I shouldn't feel them <sup>a</sup> .	2.73±1.13	2.58±1.10	0.292
36. I disapprove of myself when I have irrational ideas <sup>a</sup> .	3.06±1.09	2.31±1.05	<0.001*

\*p<0.005 is statistically significant. <sup>a</sup>Reverse-scored item.

approach is further supported as a psychological support to healthcare professionals stressed by the context of the pandemic (5,14,16).

From the results obtained, to delineate an ideal condition, one would have expected a significant increase in all items of the 4 dimensions of Mindfulness. However, this did not happen: in fact, the interviewed nurses show some aspects of Mindfulness in decrease. Therefore, the present study reinforces a need already highlighted in the literature: the increase of psychological support, as well as the strengthening of the approaches dictated by Mindfulness in order to guarantee the bio-psycho-social well-being of healthcare professionals, in particular of nurses (5). For this purpose, in the literature there are already some interventions to support the professional through above all dedicated telephone lines or the structuring of spaces (17,18) in the hospital that can favor a shaking of the whole emotional situation that the healthcare professional takes on in this particular historical period (5).

Surely this study presents the condition of 104 nurses. Future studies are desirable with a larger number of participants. Furthermore, it would be interesting to investigate if, in addition to “Before” and “During” the event, some improvement and incentive element for Mindfulness had been included in one's work environment to also try to understand which improvement factors can be more effective in imple-

menting Mindfulness skills among nursing professionals.

In conclusion, the present study is in agreement with the current literature on the need for the implementation of techniques aimed at increasing Mindfulness skills in clinical nursing practice (19,20), as this approach is effective with a cost-benefit ratio all to the advantage of both health company than professionals (21).

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WEBINARS AND CONGRESSES

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1-2 October 2021

IRCCS Mondino Foundation & University of Pavia

Pavia, Italy

**Celebrations of the 50 years of the  
Pavia Headache Centre**

*Academic Year 1970/71 - Academic Year 2020/21*

**From Research to Headache Care and Back**

and

**Ottorino Rossi Award**

**XXXI Edition**

*The event will take place in a hybrid format*



Neuropathologic University Hospital  
1917-2003



University of Pavia  
1361-2021



IRCCS Mondino Foundation,  
National Institute of Neurology  
2004-2021

## Friday 1 October

### Aula Berlucci – IRCCS Mondino Foundation

8:45

#### Welcome

- ▶ F. Svelto  
Rector, Pavia University, President C. Mondino Foundation
- ▶ L. Tronconi  
CEO, C. Mondino Foundation
- ▶ F. Blandini  
Scientific Director, C. Mondino Foundation
- ▶ G. Nappi  
Founder, Pavia Headache Centre

9:00

#### Prologue

The origins: building a solid foundation for growth (G. Sandrini, Pavia)

9:10

#### Opening Session

**Condensed lectures: from basic and clinical intuitions to translational neuroscience**

*Chairs: M.G. Buzzi (Rome), M. Ashina (Copenhagen)*

- Fifty years of pre-clinical advances (Prof. M. Moskowitz, Boston)
- Fifty years of clinical advances (Prof. J. Olesen, Copenhagen)

9:50

#### Chapter 1 - Neurons, vessels and hormones

*Chairs and discussants: G. Bono (Pavia), P. Cortelli (Bologna)*

- The dysfunctional anatomy of migraine circuitry (R. Burstein, Boston)
- Migraine and vascular disease (H-C. Diener, Essen)
- Role of gender and hormones in migraine (R. Nappi, Pavia)

11:00

Break

11:10

#### Chapter 2 - From genetics to signaling mechanisms in migraine

*Chairs and discussants: P. Geppetti (Florence), A. Genazzani (Novara)*

- Migraine and genes (A. Van den Maagdenberg, Leiden)
- The CGRP story (P.J. Goadsby, London)
- Human models of migraine (M. Ashina, Copenhagen)

12:20

#### Chapter 3 - Biomarkers of migraine: setting the path

*Chairs and discussants: G. Tedeschi (Naples), P. Calabresi (Rome)*

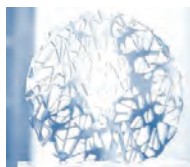
- Neuroimaging (A. May, Hamburg)
- Neurophysiology (J. Schoenen, Liège)
- Genetics (G. Terwindt, Leiden)
- Epigenetics (P. Pozo-Rosich, Barcelona)



14:30

**Ottorino Rossi Award****Lifetime achievement**

Rigmor H. Jensen (Copenhagen)

*Presenter: C. Tassorelli*

15:30

**Chapter 4 - The future of migraine research: the Pavia School continues***Chairs: G. Sandrini (Pavia), A. Costa (Pavia)*

- Animal models (C. Demartini, Pavia)
  - ▶ *Advisor: P. Goadsby (London)*
- Neurophysiological investigations (R. De Icco, Pavia)
  - ▶ *Advisor: J. Schoenen (Liège)*
- Neuromodulation (G. Cosentino, Pavia)
  - ▶ *Advisor: D. Dodick (Phoenix)*
- Neuroimaging (D. Martinelli, Pavia)
  - ▶ *Advisor: D. Borsook (Boston)*
  
- Artificial intelligence applied to migraine research (S. Figini, Pavia)

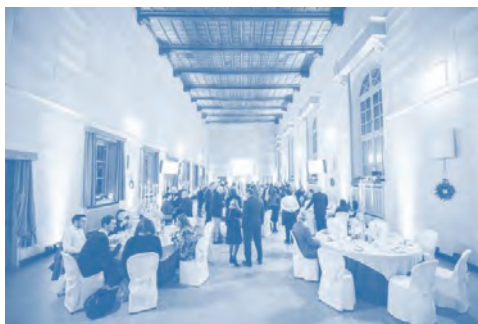
17:30

**‘Emilia Martignoni’ Memorial Award***Conferred to an Italian Junior MD, presented by Piera Martignoni*

19:30

**Hybrid Dinner****Aula Disegno, Central University Building**

- **Intermezzo** (P. Mazzarello, Pavia)  
Title TBA
  
- **Lifetime Achievement Award to Prof. Nappi** presented by T. Vecchi (Pavia)  
*(docuvideo with Prof. Nappi: 50 years in 5 milestones )*  
live webinar with colleagues and friends from Latin America



**Saturday 2 October**

**Aula Berlucci – IRCCS Mondino Foundation**

**9:00**

## Treatment of migraine and cluster headache: which options?

*Chairs: V. Guidetti, P. Martelletti (Rome)*

- Monoclonal antibodies targeting CGRP: for whom and for how long? (G. Sances, Pavia)
- Combining preventive drugs: when enough is not enough (L. Grazi, Milano)
- Gepants in migraine: blurring the lines between acute and preventive treatment (S. Guerzoni, Modena)
- Cluster headache: from neuromodulation to monoclonal antibodies (G. Coppola, Roma)

**10:30**

## Treatment of migraine and cluster headache: what matters more for the patients?

*In collaboration with AI.Ce. Group-CIRNA Foundation (30<sup>th</sup> anniversary of CIRNA)*

*Chairs: G. Sandrini, G. Sances*

- Come prevenire l'uso eccessivo di farmaci per l'attacco (N. Ghiotto, Pavia)
- Le strategie di gestione della cefalea a grappolo (M. Allena, Pavia)
- La telemedicina nella gestione del paziente cefalgico (E. Guaschino, Pavia)
- Social media e rischio di fake news (C. Di Lorenzo, Roma)
- Il punto di vista del paziente (L. Merighi, Ferrara)

Paolo Rossi Award : Winner Lecture

**12:00**

## Acknowledgements & Farewell





8-12 September 2021  
**INTERNATIONAL HEADACHE CONGRESS 2021**

**Teaching courses**

Sign up for one of our many teaching courses to broaden your knowledge of specific headache conditions or treatments.

[> Sign up for a course](#)

**Programme**

Check out the final IHC 2021 scientific programme online:

[> Online programme](#)

**OnDemand**

Missed a Session? No problem. All sessions will be available OnDemand until 13 December 2021 for all registered participants.

**First information sheet**

The most important information about the International Headache Congress 2021 at a glance.

[> Check it out](#)

**Videos**

Watch the welcome video, Zaza Katsarva's invitation and Messoud Ashina's invitation on our Homepage.

[> Videos](#)

[www.headache-congress.org](http://www.headache-congress.org)

**Advance deadline**

Don't forget to take advantage of the advance deadline registration fee and benefit from a reduced registration price until 04 August 2021.

[> Registration](#)

**Special features**

Check out the interactive segment on our congress website and for the IHC 2021 and win a free registration.

[> Special features](#)



# SISC

Società Italiana per lo Studio delle Cefalee

## PROSSIME INIZIATIVE SISC

### 35° Congresso Nazionale SISC

**Online 10-13 novembre 2021**

Scadenza invio abstract: **20 settembre 2021**

Ulteriori informazioni: [Sottomissione abstract](#)

### Scuola Superiore Interdisciplinare delle Cefalee

II Seminario - 23 ottobre 2021

**Webinar e-learning fruibile in piattaforma fino al 31 dicembre 2021**

*La Neurostimolazione nelle cefalee primarie*

Coordinatore II Seminario: Prof. Filippo Brighina

Ulteriori informazioni:

- [Programma](#)
- [Registrazione on-line](#)

### Sezioni Regionali

**Bando di concorso Sezione Triveneta SISC - Premio di Studio Giuliano Relja**

Scadenza entro le ore 8.00 del giorno 31 agosto 2021

Ulteriori informazioni: [Bando di concorso](#)

**XVII Congresso Sezione Triveneta 2021 - Emicrania**

**2.0 verso una Nuova Frontiera**

Webinar - 25/09/2021

Ulteriori informazioni: [Programma e Iscrizioni](#)

### Eventi Patrocinati

**Congresso Franciacorta Headache - 1a Edizione**

Colombaro di Cortefranca (BS) 23/09/2021 - 24/09/2021

Ulteriori informazioni: [Congresso Franciacorta Headache](#)

**44° Congresso Nazionale dell'Associazione Italiana per lo Studio del Dolore**

online 23/09/2021 - 25/09/2021

Ulteriori informazioni: [44° Congresso AISD](#)

### Altre Iniziative

**Special Issue «Headaches and Migraines during the Covid-19 Pandemic»**

Scadenza sottomissione lavori: **30 settembre 2021**

Special Issue Editor - Prof. Dr. Marina De Tommaso

Ulteriori informazioni: [https://www.mdpi.com/journal/brainsci/special\\_issues/Headaches\\_Migraines\\_COVID-19](https://www.mdpi.com/journal/brainsci/special_issues/Headaches_Migraines_COVID-19)

**La richiesta di competenza neurologica nel prossimo futuro. Quinta edizione - corso dedicato ai giovani neurologi**

Roma, 22 - 24 ottobre 2021

Ulteriori informazioni:

- [Programma e regolamento](#)
- [Scheda di iscrizione](#)



Associazione Italiana Neurologi Ambulatoriali Territoriali

**CONVEGNO**

# *Al di là del Faro*

**Nuovi orizzonti di conoscenza in Neuroscienze**



**Lloyd's Baia Hotel**

**Vietri Sul Mare, 14-16 ottobre 2021**



[www.cefalecampania.it](http://www.cefalecampania.it)

**AINATNews**

[www.ainat.it](http://www.ainat.it)



*“... misi me per l’alto mare aperto  
sol con un legno e con quella compagna  
picciola da la qual non fui deserto  
... e volta nostra poppa nel mattino  
de’ remi facemmo ali al folle volo”.*

*Dante, Divina Commedia, Inferno, Canto XXVI*



## Il nostalgico fascino del faro

*“Son notturno diamante  
che gira avvertendo gli uomini  
pei quali vivo, anche se non li vedo.  
Così, lungi da essi,  
scordati i loro nomi, li amo in moltitudini”.*

*Luis Cernuda*



Dalla terraferma veglia, quale indomita sentinella, gli sconfinati orizzonti del mare. Provvida guida per i naviganti, col suo fascino ha ammaliato la fervida fantasia di letterati e artisti, evocando immagini scolpite nelle nostre memorie: metafora della luce che rischiarava le tenebre, della conoscenza; emblema della solitudine, dell'interiorità, della ricerca di libertà.

Il suo nome deriva dall'isola greca di Pharos, su cui fu edificata una delle prime costruzioni della storia; termini simili - *Pharos, Phare, Faro* - vengono utilizzati dai popoli che vivono lungo le sponde del Mediterraneo (rispettivamente Grecia, Francia, Italia e Spagna); nei paesi anglosassoni, lo chiamano *Lighthouse (Casa della luce)*.

Già Omero nell'Iliade racconta di falò situati in cima a torri *“brillanti come lo scudo di Achille, sprigionanti un bagliore lunare che sale fino al cielo”*. Virginia Woolf lo assurge a protagonista di un suo romanzo, *Gita al faro*, del 1927; Edgar Allan Poe gli dedica un racconto, rimasto incompiuto perché colto da morte prematura; Edward Hopper, il pittore della solitudine, lo immortala in un suggestivo dipinto *Il faro di Two Lights* del 1929; il gruppo rock dei Van der Graaf Generator compone una solenne suite musicale in tema, *A Plague of Lighthouse Keepers* del 1971; *Il mare d'inverno*, una canzone interpretata dalla Bertè, lo avvolge in un'aura di solitudine e malinconia, tra *“punti invisibili rincorsi dai cani e stanche parabole di vecchi gabbiani”*.

Vi sono fari leggendari, come quello di Alessandria d'Egitto, meraviglia architettonica e tecnologica per i tempi: era alto 135 metri e il suo fuoco avvistabile fino a 56 km di distanza, distrutto da due terremoti nel corso del 1300; o anche come la *Lanterna del Molo*, ubicata nel porto di Napoli, costruita nel 1497 da re Ferdinando I, abbattuta agli inizi del secolo scorso a seguito dei lavori di ristrutturazione dell'area.



Col suo ritmo intermittente - luce, eclissi, luce - il faro “si svela e si nasconde”, come racconta Italo Svevo. Vi sono anche fari a luce fissa, come quello della Statua della Libertà a New York, inaugurato nel 1866, che per decenni ha illuminato gli spenti volti dei nostri connazionali, ivi giunti coi loro carichi di valigie di cartone e fame di speranza.

La penisola italiana ne è diffusamente costellata: dal *Faro della Vittoria* di Trieste, ancora in funzione dall’alto dei suoi 67 metri, alla iconica *Lanterna di Genova*, eretta nel 1321, che nella metà del XV secolo ebbe come guardiano Antonio Colombo, zio del marinaio Cristoforo Colombo; dal *Faro di Punta Palascia*, a capo d’Otranto, il punto più orientale d’Italia, alla *Lanterna di Montorsoli* di Messina, una torre di tre piani edificata nel XVI secolo.

Una specie in via di estinzione, soppiantata dalla moderna tecnologia digitale: la sua sorte è andare in disuso o svolgere nuove funzioni. Così il *Faro di Montauk Point* nel Long Island, il primo nella storia degli Stati Uniti, fatto edificare da George Washington, è diventato di recente un museo; di contro, quello di *Corsewall*, nella Scozia meridionale, costruito nel 1815, è stato trasformato in un lussuoso hotel. E con esso è tramontata anche la mitica figura del guardiano del faro, immortalata nei versi di poeti quali Luis Cernuda o in romanzi, quale *Il faro in capo al mondo* di Jules Verne, pubblicato postumo nel 1905.

Nel nostro immaginario, il faro è luce che ispira, l’orientamento di cui ciascuno ha bisogno - parafrasando Dante - per non dover “*negare l’esperienza*”, vale a dire la conoscenza. La parola “*esperienza*” ha un doppio significato: “*provare*” (lett. “*uscire fuori di sé*”) ma anche “*mettersi alla prova*”, dalla radice “*per*” (dove il termine *pericolo*), in riferimento alla possibilità di “*perdersi*” nel vagare “*per l’alto mare aperto*”.

Accogliendo l’invito di Ulisse, “*uniti in un sol legno*” siamo pronti a compiere il “*folle volo*”. Dalla terraferma, lampi di luce fendono l’aere bruno, a dirci che il faro è certezza, nostalgia, ricordo, attesa. E’ direzione, non punto di arrivo. L’idealità: ciò che ci muove verso l’imperscrutabile e lo rende chiaro ai nostri occhi.



## *“Non vogliate negar l'esperienza”*

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Obiettivo di questo meeting è quello di fornire aggiornamenti in merito a patologie di primario interesse per il neurologo clinico, quali Parkinson, demenza, epilessia e cefalee, con particolare attenzione rivolta ai più recenti trattamenti, farmacologici e non, resi possibili grazie a una maggiore comprensione dei meccanismi fisiopatologici e biomolecolari che le sottendono.

Non mancheranno riferimenti sia a malattie rare, quali la SMA nell'adulto, sia a nuovi settori in rapida espansione, quale quello relativo alla Nutraceutica, di cui saranno analizzati i rapporti tra evidenze cliniche e best practice.

Uno spazio sarà dedicato alla discussione sulle possibili modalità di organizzazione ed implementazione di una rete che ottimizzi l'assistenza al paziente neurologico cronico nell'ottica dei cambiamenti e delle sfide poste dalla pandemia da COVID19 al nostro Sistema sanitario.

Un Simposio sul tema dell'umana fragilità esplorerà questa "virtù dimenticata" nei suoi principali aspetti - etici, esistenziali e sociali - a testimoniare lo stretto legame esistente tra Scienze umane e Neuroscienze.

**"Al di là del faro":** un titolo suggestivo per un evento altamente proficuo per l'aggiornamento professionale, che chiama a raccolta studiosi di varia formazione - umanisti, neuro-scienziati e clinici - ossequiosi all'ardente invito dantesco a inoltrarsi, in maniera congiunta, verso gli sconfinati orizzonti di un sapere condiviso e perseguito con slancio vitale.

## Diario di viaggio



***“Il mare è così grande, Signore,  
e la mia barca così piccola”.***

***Preghiera del marinaio nella tempesta***



## Prima giornata



*“Il faro era la torre della pace, dell’ospitalità benevolente... La sua posizione di guardiano dei mari, di vigilatore costante dello stretto, ne facevano una persona”.*

*Jules Michelet, Il mare*



**Giovedì, 14 ottobre 2021**

**Ore 9.30**

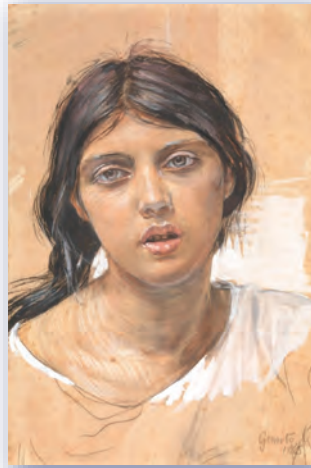
**SIMPOSIO SATELLITE**

*“Come turchese in mezzo a fitte perle”*

**LA GRAZIA DELLA FRAGILITÀ: UN PERCORSO ENTRO LE SCIENZE UMANE**

*“Era tenero e fine il suo sorriso  
come brillio d'antico avorio,  
come nostalgia,  
come neve che a Natale  
sull'oscuro villaggio discende,  
come turchese in mezzo a fitte perle,  
come raggio di luna  
su un caro libro”.*

*Rainer Maria Rilke*



**9.30 Introduzione ai lavori:** *Alfonso Tortora*

**9.40-11.30 I SESSIONE – OLTRE LA FRAGILITÀ**

Moderatori: *Carlo Montinaro (Nocera), Alfonso Tortora (Salerno)*

Semantica della fragilità, *Domenico Cassano*

**Lettura Magistrale**

Storia della fragilità: frammenti e tappe di un percorso culturale, *Aurelio Musi*

(Ab)uso di anglicismi: un fenomeno di fragilità linguistica? Studio contrastivo italiano-francese, *Nicla Mercurio*

**Lettura Magistrale**

Antropologia della fragilità: le quattro virtù per combattere il COVID, *Franco Salerno*

Dalla fragilità alla logica del bene comune: la lezione di Antonio Genovesi, *Nicla Iacovino*

**Coffee Break**

**12.00-13.30 II SESSIONE – UNA VIRTU' NASCOSTA**

Moderatori: *Anna Maria Mugnano (Napoli), Maria Tagliamonte (Pagani)*

Ri-conoscere la malinconia: la depressione negli annali del manicomio consortile di Nocera, *Giuseppina Salomone*

Verso la luce: l'esperienza mistica, *Luigino Rossi*

L'anziano fragile, *Ferdinando Pellegrino*

Per una controcultura della rottamazione: il futuro è nel sapere dell'anziano, *Domenico Cassano*

I nuovi orizzonti: i diritti delle persone con disabilità alla luce dei nuovi provvedimenti legislativi e della Convenzione ONU, *Vincenzo Galatro*

**13.30 Fine dei lavori**

**Giovedì, 14 ottobre 2021****Ore 14.00****14.00 Apertura dei lavori - Saluto delle Autorità****14.30 Lettura Magistrale**Presentazione: *Franco Lucchese (Roma)*

Why would you become a medical leader? A study of the driving forces among the first line medical leaders during the Covid-19 pandemia, *Max Rapp Ricciardi (Gothenburg, Sweden)*

**15.00-16.00 LA GESTIONE DELLO STROKE ISCHEMICO**Moderatori: *Vincenzo Andreone (Napoli), Antonino Pavone (Catania)*Dalle statine agli inibitori del PCSK9, *Franco Guarnaccia (Napoli)***Lettura Magistrale**Ictus criptogenetico: la fibrillazione atriale e il ruolo del loop recorder, *Lucio D'Anna (Londra)***16.00-17.30 UPDATE IN EPILESSIA**Moderatori: *Francesco Habetswallner (Napoli), Enrico Volpe (Napoli)*Epilessia farmaco-resistente, *Marianna Pezzella (Napoli)*Le caratteristiche del farmaco ideale in *first add on*, *Pietro Penza (Salerno)*La gestione delle crisi in emergenza, *Francesca Conte (Napoli)***17.30-19.00 MALATTIA DI PARKINSON: UN UPDATE**Moderatori: *Bruno Ronga (Napoli), Maddalena Terracciano (Napoli)*

Il ruolo degli inibitori enzimatici nel trattamento della Malattia di Parkinson, *Carlo Alberto Mariani (Palermo)*

Terapie avanzate nel morbo di Parkinson, *Marcello Esposito (Napoli)*Le terapie infusionali: Levodopa in gel, Apomorfina e future prospettive, *Mario Di Giovanni (Napoli)*

L'importanza della riabilitazione nel processo di rete assistenziale per i disordini del movimento, *Pietro Marano (Enna)*

**19.00 Cocktail di benvenuto**

## Seconda giornata



*“Ora eravamo molto vicini al Faro. Eccoli che si stagiava, nudo e dritto, abbagliante di bianco e nero, e si vedevano le onde rompersi in schegge bianche come vetro infranto contro gli scogli. Si vedevano chiaramente le finestre; un tocco di bianco su una di esse e un ciuffo di verde sullo scoglio. Un uomo era uscito, ci aveva guardati con il cannocchiale ed era rientrato. Ecco com’era il Faro che per tutti quegli anni avevamo visto attraverso la baia: una torre nuda su una roccia deserta con un occhio giallo che si apriva all’improvviso e dolcemente la sera”.*

*Virginia Woolf, Gita al Faro*



## Venerdì, 15 ottobre 2021



**9.00** Apertura dei lavori

### **9.10-11.30 UPDATE IN TEMA DI CEFALEE**

Moderatori: *Assunta Tarsitano (Cosenza), Giovanna Trevisi (Lecce)*

Dalla tossina botulinica alle nuove formulazioni e combinazioni con Triptani, *Maria Cristina Lerza (Eboli), Domenico Cassano (Nocera Inf.)*

Ditani e Gepanti, *Teresa Catarci (Roma)*

#### **Lettura Magistrale**

Il ruolo del CGRP nella patogenesi dell'emicrania: dalla ricerca di base alle nuove terapie con anticorpi monoclonali, *Piero Barbanti (Roma)*

La target therapy nel paziente emicranico, *Franca Moschiano (Napoli)*

#### **Lettura Magistrale**

Gestione della cefalea e COVID: il ruolo della Telemedicina, *Franco Lucchese (Roma)*

### **11,30 Coffee Break**

### **Ore 12.00-14.00 LA NUTRACEUTICA TRA MITO E SCIENZA**

Moderatori: *Roberto Tramutoli (Roma), Maria Esposito (Napoli)*

#### **Ore 12.00-13.30 - I PARTE**

##### **Lecture magistrali**

Nutraceutica e resilienza, *Daniele Mei (Viterbo)*

Equilibrio dell'ecosistema intestinale e malattie neurologiche, *Gerardo Nardone (Napoli)*

Cefalea e nutraceutica in età evolutiva, *Marco Carotenuto (Napoli)*

Nutraceutica e cefalee primarie in età adulta, *Vincenzo Pizza (Vallo della Lucania)*



#### 14.30-15.30 - II PARTE

In attesa dei farmaci "disease modifying": ruoli e utilità della Nutraceutica nelle demenze, *Lorenzo Cipriano (Napoli)*

Il ruolo delle Coline nel declino cognitivo, *Pietro Gareri (Catanzaro)*

#### 15.30-16.30 IL DECLINO COGNITIVO: UN UPDATE

Moderatori: *Cinzia Coppola (Napoli), Carmine Fuschillo (Napoli)*

Confronto tra aspetti clinici e neurobiologici delle demenze, *Pasquale Alfieri (Napoli)*

Fasi precoci del declino cognitivo tra Disturbo Soggettivo della Memoria (SCD) e Disturbo Cognitivo Lieve (MCI), *Umberto Ruggiero (Napoli)*

#### 16.30-18.00 IL TERRITORIO, L'IDEALE REALIZZABILE

Moderatori: *Carlo Alberto Mariani (Palermo), Mauro Palumbo (Bari)*

Problematiche socio-familiari nella gestione domiciliare dell'Alzheimer in fase avanzata, *Giovanna Trevisi (Lecce)*

La neurologia del territorio tra Sanita' elettronica, setting sanitari e socio-assistenziali, *Vito Napolitano (Bari)*

La rete assistenziale di cure palliative: l'assistenza domiciliare al paziente neurologico, *Assunta Tarsitano (Cosenza)*

**TAVOLA ROTONDA** - Le nuove sfide della Medicina del Territorio: Telemedicina e Prescrivibilità dei farmaci con nota. Stato dell'arte e prospettive

**Moderatori:** *Gennaro Cascone (Pompei), Raffaele Galano (Salerno)*

Con: *Vincenzo Santomauro (SAPMI), Daniela Postiglione (SUMAI), Vincenzo Del Pizzo (Farmacia Territoriale ASL SA), Umberto Ruggiero (Napoli), Pasquale Alfieri (Napoli)*

#### Coffee Break

#### 18.00-19.00 DEPRESSIONE E DISTURBI DEL SONNO: UN UPDATE

Moderatori: *Gennaro Cascone (Pompei), Rosa Di Donato (Gagnano)*

Depressione e trattamento: un update, *Fausto Sorrentino (C. Mare di Stabia)*

Disturbi del sonno: dalla diagnosi alla terapia farmacologica, *Rossana Arlomede (Napoli)*

#### 18.30 Chiusura dei Lavori



## Terza giornata



*“Quando guardo i fari... mi allontanano nello spazio e vado in luoghi remoti. Mi allontanano anche nel tempo, verso un passato che so di idealizzare, in cui la solitudine era più semplice. Mi discosto anche dai gusti del mio tempo perché oggi i fari sembrano figure romantiche e sublimi, due parole passate di moda”.*

*Jazmina Barrera, Quaderno dei fari*



## Sabato, 16 ottobre 2021



### 9.00-10.00 I DISTURBI DELL'EQUILIBRIO: UN UPDATE

Moderatori: *Sabato Leo (Scafati), Pietro Marano (Enna)*

#### Letture Magistrali

Il ruolo del Vestibologo, *Vincenzo Marcelli (Napoli)*

La gestione combinata: il ruolo del Neurologo, *Domenico Cassano (Nocera Inf.)*

### 10.00-11.00 ATROFIA MUSCOLARE SPINALE: UN UPDATE

Moderatori: *Antonella Toriello (Salerno), Vincenzo Busillo (Eboli)*

La SMA nell'adulto: segni e sintomi, *Lucia Ruggiero (Napoli)*

Il ruolo dell'EMG nelle patologie neuro-muscolari, *Maria Cristina Lerza (Eboli)*

**Discussione:** Il Territorio-l'Ospedale: la presa in carico condivisa del paziente con SMA

### 11.00 LETTURA MAGISTRALE

Le memorie, le attese, i progetti futuri. Un amarcord di *Vincenzo Guidetti (Roma)*

### 11.30-12.00 Coffee Break

### 12.00-13.30 LA NEUROLOGIA IN ERA COVID

Moderatori: *Vincenzo Mascia (Cagliari), Angela Trotta (Salerno)*

Quadri clinici di cefalea in era COVID, *Maria Pia Prudenzeno (Bari)*

Sclerosi multipla in era COVID: tra dubbi e realtà, *Vincenzo Busillo (Eboli)*

Deficit cognitivi nel Post-COVID, *Vincenzo Mascia (Cagliari)*

COVID 19 e sindrome di Guillain Barrè, *Clotilde Ciampa (Napoli)*

### 13.00-13.30 Discussione e Chiusura dei lavori

## Faculty



- |  |   |
|--|---|
| <b>Pasquale Alfieri</b> ( <i>Napoli</i> )        | <b>Pietro Marano</b> ( <i>Catania</i> )               |
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## Illustrazioni



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## L'approdo

***"Terra, terra, terra!"***  
*Rodrigo de Triana*



***Quale sarà l'ultima nave che giungerà in porto grazie alla luce di un faro?  
Chi sarà l'ultimo guardiano del mondo?  
Ci sarà ancora un tempo in cui qualcuno accenderà una luce per i naviganti  
che ne avranno bisogno? ...***





***... Forse saranno i fari stessi a illuminarsi come templi  
in ricordo di tutti coloro che giacciono in fondo al mare.***

**Dedicato a**

***Sergio Allocca, Antonello Crisci, Dario Grossi,  
Giuseppe Liguori, Carlo Lisotto, Paolo Rossi***



## Book reviews



### **L'intrigo Spallanzani**

di Paolo Mazzarello

Edizione: Bollati Boringhieri

Il leggendario mago della sperimentazione, Lazzaro Spallanzani, era un affermato professore di storia naturale a Pavia quando nel 1785 decise di compiere una lunga esplorazione nei territori dell'impero ottomano. Durante l'avventuroso viaggio fece notevoli osservazioni di biologia marina, geologia e ornitologia. Con il fervore di una mente insaziabile, annotò gli usi delle popolazioni locali e l'amalgama di splendore e fatiscenza delle città, partecipando alla vivace vita culturale che ruotava attorno alle ambasciate occidentali.

Quando fece ritorno a Pavia, venne investito dall'accusa infamante di aver rubato degli esemplari naturalistici dal museo dell'Università. Alla base di questo complotto vi erano invidie e rivalità accademiche, non così distanti da quelle odierne, ma anche forti contrapposizioni ideologiche. Caduta ogni accusa, la vicenda si concluse con la vendetta dello scienziato ai danni del suo principale detrattore, Giovanni Antonio Scopoli: una rivincita che, tramite reperti finti e sagaci libretti pseudonimi, presentava la stessa precisione e verve creativa delle sue indagini scientifiche.

Gli intrighi dei celebri accademici divennero famosi anche all'estero e – come svelano alcuni recenti ritrovamenti documentali – si spinsero fino all'entourage di un anziano Carlo Goldoni.

Paolo Mazzarello allestisce una formidabile impalcatura di fonti, restituendo con uno stile garbato e ironico l'esuberante atmosfera del secolo dei Lumi. Un impareggiabile viaggio nella cultura scientifica dell'Italia del Settecento fra sfide della scienza e congiure di potere.



### **Explaining Health Across the Sciences**

di Jonathan Sholl, Suresh I. S. Rattan (Editors)

Edizione: Springer

Rapidly changing demographics worldwide towards increased proportion of the elderly in the population and increased life-expectancy have brought the issues, such as “why we grow old”, “how we grow old”, “how long can we live”, “how to maintain health”, “how to prevent and treat diseases in old age”, “what are the future perspectives for healthy ageing and longevity” and so on, in the centre stage of scientific, social, political, and economic arena. Although the descriptive aspects of ageing are now well established at



the level of species, populations, individuals, and within an individual at the tissue, cell and molecular levels, the implications of such detailed understanding with respect to the aim of achieving healthy ageing and longevity are ever-changing and challenging issues. This continuing success of gerontology, and especially of biogerontology, is attracting the attention of both the well established academicians and the younger generation of students and researchers in biology, medicine, bioinformatics, bioeconomy, sports science, and nutritional sciences, along with sociologists, psychologists, politicians, public health experts, and health-care industry including cosmeceutical-, food-, and lifestyle-industry. Books in this series will cover the topics related to the issues of healthy ageing and longevity. This series will provide not only the exhaustive reviews of the established body of knowledge, but also will give a critical evaluation of the ongoing research and development with respect to theoretical and evidence-based practical and ethical aspects of interventions towards maintaining, recovering and enhancing health and longevity. More information about this series at <http://www.springer.com/series/13277>

# circadin®

Melatonina a Rilascio Prolungato 2mg



## RIASSUNTO DELLE CARATTERISTICHE DEL PRODOTTO

### 1. DENOMINAZIONE DEL MEDICINALE

Circadin 2 mg compresse a rilascio prolungato.

### 2. COMPOSIZIONE QUALITATIVA E QUANTITATIVA

Ogni compressa a rilascio prolungato contiene 2 mg di melatonina.

Eccipiente con effetti noti: ogni compressa a rilascio prolungato contiene 80 mg di lattosio monoidrato.

Per l'elenco completo degli eccipienti, vedere paragrafo 6.1.

### 3. FORMA FARMACEUTICA

Compressa a rilascio prolungato.

Compresse rotonde, biconvesse, di colore da bianco a biancastro.

### 4. INFORMAZIONI CLINICHE

#### 4.1 Indicazioni terapeutiche

Circadin è indicato come monoterapia per il trattamento a breve termine dell'insonnia primaria caratterizzata da una qualità del sonno scadente in pazienti da 55 anni di età.

#### 4.2 Posologia e modo di somministrazione

##### Posologia

La dose raccomandata è di una compressa da 2 mg una volta al giorno, 1-2 ore prima di coricarsi e dopo aver mangiato. Tale dosaggio può essere mantenuto per un periodo fino a tredici settimane.

##### Popolazione pediatrica

La sicurezza e l'efficacia di Circadin nei bambini di età compresa tra 0 e 18 anni non sono state ancora stabilite.

Non ci sono dati disponibili.

##### Compromissione renale

Non è stato studiato l'effetto della compromissione renale a qualunque stadio sulla farmacocinetica della melatonina. Di conseguenza è necessario usare particolare cautela durante la somministrazione di melatonina a questa categoria di pazienti.

##### Compromissione epatica

Non c'è esperienza sull'uso di Circadin nei pazienti con compromissione epatica. I dati pubblicati dimostrano livelli marcatamente elevati di melatonina endogena durante le ore diurne a causa della clearance ridotta nei pazienti con compromissione epatica. Pertanto l'uso di Circadin non è raccomandato nei pazienti con compromissione epatica.

##### Modo di somministrazione

Uso orale. Le compresse devono essere deglutite intere per conservare le proprietà di rilascio prolungato. Evitare lo schiacciamento o la masticazione per agevolare l'ingestione.

#### 4.3 Controindicazioni

Ipersensibilità al principio attivo o ad uno qualsiasi degli eccipienti elencati al paragrafo 6.1.

#### 4.4 Avvertenze speciali e precauzioni di impiego

Circadin può causare sonnolenza. Pertanto il medicinale deve essere utilizzato con cautela qualora gli effetti della sonnolenza possano rappresentare un rischio per la sicurezza del paziente.

Non esistono dati clinici circa l'uso di Circadin in pazienti con malattie auto-immuni. Pertanto l'uso di Circadin non è raccomandato nei pazienti con malattie auto-immuni.

Circadin contiene lattosio. I pazienti con rari problemi ereditari di intolleranza al galat-

tosio, deficit della LAPP lattasi o sindrome da malassorbimento di glucosio-galattosio non devono assumere questo medicinale.

#### 4.5 Interazioni con altri medicinali ed altre forme di interazione

Sono stati effettuati studi di interazione solo negli adulti.

##### Interazioni farmacocinetiche

- È stato osservato che la melatonina induce il CYP3A *in vitro* se somministrata in concentrazioni sovratrapieutiche. La rilevanza clinica di tale osservazione non è nota. In caso di induzione enzimatica, si può determinare una diminuzione delle concentrazioni plasmatiche di altri medicinali somministrati contemporaneamente.
- La melatonina non induce gli enzimi CYP1A *in vitro* se somministrata in concentrazioni sovratrapieutiche. Pertanto, le interazioni tra melatonina ed altri principi attivi dovute all'effetto della melatonina sugli enzimi CYP1A probabilmente non sono significative.
- Il metabolismo della melatonina è mediato principalmente dagli enzimi CYP1A. Pertanto, è possibile un'interazione tra la melatonina ed altri principi attivi dovuta al loro effetto sugli enzimi CYP1A.
- È necessario usare particolare cautela nei pazienti trattati con fluvoxamina, che aumenta i livelli di melatonina (fino a 17 volte l'AUC e 12 volte la  $C_{max}$  sierica) attraverso l'inibizione del suo metabolismo da parte degli isoenzimi epatici CYP1A2 e CYP2C19 del citocromo P450 (CYP). L'associazione tra queste sostanze deve essere evitata.
- È necessario usare particolare cautela nei pazienti trattati con 5- o 8-metossipsoralene (5 e 8-MOP), poiché aumentano i livelli di melatonina attraverso l'inibizione del suo metabolismo.
- È necessario usare particolare cautela nei pazienti trattati con cimetidina, un inibitore del CYP2D, poiché aumenta i livelli plasmatici di melatonina attraverso l'inibizione del suo metabolismo.
- Il fumo di sigaretta può diminuire i livelli di melatonina attraverso l'induzione del CYP1A2.
- È necessario usare particolare cautela nei pazienti trattati con estrogeni (ad esempio contraccettivi o terapia ormonale sostitutiva), poiché aumentano i livelli di melatonina attraverso l'inibizione del suo metabolismo da parte del CYP1A1 e del CYP1A2.
- Gli inibitori del CYP1A2 come i chinoloni possono determinare un'aumentata esposizione alla melatonina.
- Gli induttori del CYP1A2 come carbamazepina e rifampicina possono determinare ridotte concentrazioni plasmatiche di melatonina.
- Sono disponibili molti dati di letteratura circa gli effetti degli agonisti/antagonisti adrenergici, degli agonisti/antagonisti oppiacei, degli antidepressivi, degli inibitori delle prostaglandine, delle benzodiazepine, del triptofano e dell'alcol sulla secrezione di melatonina endogena. Non è stato studiato se questi principi attivi interferiscono con gli effetti dinamici o cinetici di Circadin o viceversa.

##### Interazioni farmacodinamiche

- Non deve essere consumato alcool in associazione con Circadin, poiché questo riduce l'efficacia di Circadin sul sonno.
- Circadin può potenziare le proprietà sedative delle benzodiazepine e degli ipnotici non benzodiazepinici quali zaleplon, zolpidem e zopiclone. In uno studio clinico, è emersa una chiara evidenza di interazione farmacodinamica transitoria tra Circadin e zolpidem un'ora dopo la loro somministrazione concomitante. La somministrazione concomitante si è tradotta in una maggiore riduzione dell'attenzione, della memoria e della coordinazione rispetto alla somministrazione di zolpidem da solo.
- In altri studi, Circadin è stato somministrato in associazione con tioridazina ed imipramina, principi attivi che agiscono sul sistema nervoso centrale. Non sono state osservate interazioni farmacocinetiche clinicamente significative in nessuno dei due studi. Tuttavia, la contemporanea somministrazione di Circadin ha comportato un maggiore senso di tranquillità ed una maggiore difficoltà a svol-

gere compiti rispetto ad imipramina da sola, ed una maggiore sensazione di pesantezza nella testa ("muzzy-headedness") rispetto alla tioridazina da sola

#### 4.6 Fertilità, gravidanza e allattamento

##### Gravidanza

Non sono disponibili dati clinici relativi all'assunzione di melatonina durante la gravidanza. Gli studi sugli animali non indicano effetti dannosi diretti o indiretti su gravidanza, sviluppo embrionale/fetale, parto o sviluppo post-natale (vedere paragrafo 5.3). A causa della mancanza di dati clinici, non si raccomanda l'uso del medicinale in donne in gravidanza o che intendono intraprendere una gravidanza.

##### Allattamento

Melatonina endogena è stata rilevata nel latte materno, quindi probabilmente melatonina esogena è escreta nel latte materno. Esistono dati su modelli animali tra cui roditori, ovini, bovini e primati, che indicano un passaggio di melatonina dalla madre al feto attraverso la placenta o il latte. Pertanto, l'allattamento non è raccomandato per le donne trattate con melatonina.

#### 4.7 Effetti sulla capacità di guidare veicoli e sull'uso di macchinari

Circadin altera lievemente la capacità di guidare veicoli o di usare macchinari.

Circadin può causare sonnolenza, pertanto deve essere utilizzato con cautela qualora gli effetti della sonnolenza possano rappresentare un rischio per la sicurezza.

#### 4.8 Effetti indesiderati

##### Riassunto del profilo di sicurezza

Negli studi clinici (nei quali, complessivamente, 1.931 pazienti sono stati trattati con

Circadin e 1.642 pazienti hanno ricevuto placebo), il 48,8% dei pazienti trattati con Circadin ha riportato una reazione avversa rispetto al 37,8% dei pazienti trattati con placebo. Se si confronta la percentuale dei pazienti che hanno riportato una reazione avversa rispetto alle 100 settimane-paziente, il valore è più alto per il placebo che per Circadin (5,743 – placebo - vs. 3,013 – Circadin). Le reazioni avverse più comuni sono state cefalea, nasofaringite, dolore alla schiena ed artralgia, reazioni considerate comuni, secondo la classificazione MedDRA, sia nel gruppo trattato con Circadin che in quello trattato con placebo.

##### Elenco in forma tabellare delle reazioni avverse

Negli studi clinici e nelle segnalazioni spontanee post-marketing sono state riportate le seguenti reazioni avverse.

All'interno degli studi clinici, complessivamente il 9,5% dei pazienti trattati con Circadin ha riportato una reazione avversa rispetto al 7,4% dei pazienti trattati con placebo. Si riportano di seguito soltanto reazioni avverse verificatesi durante gli studi clinici nei pazienti, con frequenza pari o superiore a quanto osservato nei pazienti trattati con placebo.

All'interno di ciascuna classe di frequenza, gli effetti indesiderati sono riportati in ordine decrescente di gravità.

Le frequenze sono definite come Molto comune ( $\geq 1/10$ ); Comune ( $\geq 1/100$ ,  $<1/10$ ); Non comune ( $\geq 1/1.000$ ,  $<1/100$ ); Raro ( $\geq 1/10.000$ ,  $<1/1.000$ ); Molto raro ( $<1/10.000$ ); Non nota (la frequenza non può essere definita sulla base dei dati disponibili).

##### Segnalazione delle reazioni avverse sospette

La segnalazione delle reazioni avverse sospette che si verificano dopo l'autorizzazione

Classificazione per sistemi e organi	Molto comune	Comune	Non comune	Raro	Non nota: (la frequenza non può essere definita sulla base dei dati disponibili)
Infezioni ed infestazioni				Herpes zoster	
Patologie del sistema emolinfopoietico				Leucopenia, trombocitopenia	
Disturbi del sistema immunitario					Reazione di ipersensibilità
Disturbi del metabolismo e della nutrizione				Ipertrigliceridemia, ipocalcemia, iponatremia	
Disturbi psichiatrici			Irritabilità, nervosismo, irrequietezza, insonnia, sogni anomali, incubi, ansia	Alterazioni dell'umore, aggressività, agitazione, pianto, sintomi di stress, disorientamento, risveglio precoce mattutino, aumento della libido, umore depresso, depressione	
Patologie del sistema nervoso			Emicrania, cefalea, letargia, iperattività psicomotoria, capogiro, sonnolenza	Sincope, deficit di memoria, disturbi dell'attenzione, stato sognante, sindrome delle gambe senza riposo, sonno di qualità scadente, parestesie	
Patologie dell'occhio				Diminuita acuità visiva, visione offuscata, aumentata lacrimazione	
Patologie dell'orecchio e del labirinto				Vertigine posturale, vertigini	
Patologie cardiache				Angina pectoris, palpitazioni	
Patologie vascolari			Iperensione	Vampate di calore	
Patologie gastrointestinali			Dolore addominale, dolore della parte superiore dell'addome, dispepsia, ulcerazioni nella bocca, bocca secca, nausea	Malattia da reflusso gastroesofageo, disordini gastrointestinali, vescicazione della mucosa orale, ulcerazione della lingua, disturbi gastrointestinali, vomito, suoni gastrointestinali anormali, flatulenza, ipersecrezione salivare, alitosi, disagio addominale, disturbi gastrici, gastrite	

Classificazione per sistemi e organi	Molto comune	Comune	Non comune	Raro	Non nota: (la frequenza non può essere definita sulla base dei dati disponibili)
Patologie epatobiliari			Iperbilirubinemia		
Patologie della cute e del tessuto sottocutaneo			Dermatite, sudorazione notturna, prurito, rash, prurito generalizzato, secchezza cutanea	Eczema, eritema, dermatite alle mani, psoriasi, rash generalizzato, rash pruriginoso, disturbi a carico delle unghie	
Patologie del sistema muscoloscheletrico e del tessuto connettivo			Dolori alle estremità	Artrite, spasmi muscolari, dolore al collo, crampi notturni	Angioedema, edema della bocca, edema della lingua
Patologie renali e urinarie			Glicosuria, proteinuria	Poliuria, ematuria, nicturia	
Patologie dell'apparato riproduttivo e della mammella			Sintomi di menopausa	Priapismo, prostatite	
Patologie sistemiche e condizioni relative alla sede di somministrazione			Astenia, dolore toracico	Affaticamento, dolore, sete	Galattorrea
Esami diagnostici			Anomalie dei test di funzionalità del fegato, aumento del peso corporeo	Aumento degli enzimi epatici, anomalie degli elettroliti nel sangue, anomalie dei test di laboratorio	

del medicinale è importante in quanto permette un monitoraggio continuo del rapporto beneficio/rischio del medicinale. Agli operatori sanitari è richiesto di segnalare qualsiasi reazione avversa sospetta tramite il *sistema nazionale di segnalazione riportato nell'Allegato V*.

#### 4.9 Sovradosaggio

Sono stati riferiti diversi casi di sovradosaggio dopo la commercializzazione del medicinale. La sonnolenza ha rappresentato l'evento avverso riferito con maggiore frequenza. Nella maggior parte dei casi l'intensità di tale evento è stata da lieve a moderata. In studi clinici, Circadin è stato somministrato al dosaggio di 5 mg al giorno per 12 mesi senza alterare significativamente la natura delle reazioni avverse segnalate. È riportata in letteratura la somministrazione di dosi quotidiane fino a 300 mg di melatonina senza causare reazioni avverse clinicamente significative.

In caso di sovradosaggio è prevedibile che si verifichi sonnolenza. La clearance del principio attivo si verifica entro 12 ore dall'ingestione. Non è richiesto alcun trattamento specifico.

### 5. PROPRIETÀ FARMACOLOGICHE

#### 5.1 Proprietà farmacodinamiche

Categoria farmacoterapeutica: Psicolettici, agonisti dei recettori della melatonina, codice ATC: N05CH01. La melatonina è un ormone naturale prodotto dall'epifisi, strutturalmente legata alla serotonina. Da un punto di vista fisiologico, la secrezione di melatonina aumenta poco dopo l'esordio del buio, raggiunge il massimo tra le ore 2 e 4 del mattino e diminuisce nella seconda metà della notte. La melatonina è associata al controllo del ritmo circadiano ed alla sincronizzazione al ciclo luce-buio. Essa è anche associata ad un effetto ipnotico e ad un'augmentata propensione al sonno.

#### Meccanismo d'azione

Si ritiene che l'attività della melatonina a livello dei recettori MT1, MT2 e MT3 contribuisca alle sue proprietà di favorire il sonno, in quanto tali recettori (soprattutto MT1 e MT2) svolgono un ruolo nella regolazione del ritmo circadiano e del sonno.

#### Razionale d'uso

Considerando sia il ruolo della melatonina nel sonno e nella regolazione del ritmo circadiano, che la diminuzione della secrezione di melatonina endogena in relazione all'età, la melatonina può migliorare in maniera efficace la qualità del sonno in particolar modo nei pazienti d'età pari o superiore a 55 anni che soffrono di insonnia primaria.

#### Efficacia e sicurezza clinica

Negli studi clinici nei quali i pazienti che soffrivano di insonnia primaria hanno ricevuto Circadin 2 mg ogni sera per 3 settimane sono stati osservati dei miglioramenti

nei pazienti trattati con il medicinale, rispetto ai pazienti trattati con placebo in termini di latenza del sonno (misurata con strumenti sia obiettivi che soggettivi), qualità soggettiva del sonno e funzionalità durante il giorno (sonno ristoratore) senza alcun deficit della vigilanza durante il giorno. In uno studio polisonnografico (PSG) con un periodo di run-in di 2 settimane (studio singolo-cieco con placebo), seguito da un periodo di trattamento di 3 settimane (doppio-cieco, controllato con placebo, a gruppi paralleli) ed un periodo di sospensione di 3 settimane, la latenza del sonno è risultata accorciata di 9 minuti rispetto a quanto osservato con placebo. Con Circadin non sono state osservate alterazioni nell'architettura del sonno e nessun effetto sulla durata del sonno REM (Rapid Eye Movement). Con Circadin 2 mg non si è verificata alcuna modifica nelle funzioni diurne.

In uno studio su pazienti ambulatoriali con un periodo basale di run-in di 2 settimane con placebo, un periodo di 3 settimane di trattamento randomizzato, in doppio-cieco, controllato con placebo, a gruppi paralleli ed un periodo di sospensione di 2 settimane con placebo, la percentuale di pazienti che hanno manifestato un miglioramento clinicamente significativo sia della qualità del sonno che nella vigilanza al mattino è stata del 47% nel gruppo trattato con Circadin contro il 27% nel gruppo trattato con placebo. Inoltre, la qualità del sonno e la vigilanza al mattino sono risultate significativamente migliorate con Circadin rispetto a placebo. Le variabili del sonno sono ritornate gradualmente ai valori iniziali, senza effetto rebound, e senza alcun aumento delle reazioni avverse o sintomi da sospensione.

In un secondo studio su pazienti ambulatoriali con un periodo basale di run-in di 2 settimane con placebo, seguito da un periodo di 3 settimane di trattamento randomizzato, in doppio-cieco, controllato con placebo, a gruppi paralleli, la percentuale di pazienti che ha manifestato un miglioramento clinicamente significativo sia della qualità del sonno che nella vigilanza al mattino è stata del 26% nel gruppo trattato con Circadin contro il 15% nel gruppo trattato con placebo. Circadin ha diminuito la latenza del sonno riferita dai pazienti di 24,3 minuti contro 12,9 minuti per i pazienti trattati con placebo. Inoltre la qualità del sonno, il numero di risvegli e lo stato di vigilanza al mattino riferiti dai pazienti sono migliorati significativamente con Circadin rispetto a placebo. La qualità della vita è migliorata in misura significativa con Circadin 2 mg rispetto a quanto osservato con placebo. Un'altra sperimentazione clinica randomizzata (n=600) ha confrontato gli effetti di Circadin e placebo per un massimo di sei mesi. I pazienti sono stati nuovamente randomizzati alla settimana 3. Lo studio ha dimostrato dei miglioramenti nella latenza del sonno, nella qualità del sonno e nello stato di vigilanza al mattino, senza alcun sintomo da sospensione né insonnia rebound. Lo studio ha dimostrato che i benefici osservati dopo 3 settimane venivano mantenuti fino a 3 mesi ma il set di analisi primaria a 6 mesi non è stato superato. A 3 mesi, il numero di pazienti responsivi nel gruppo trattato con Circadin era di circa 10% in più.

## 5.2 Proprietà farmacocinetiche

### Assorbimento

L'assorbimento della melatonina assunta per via orale è completo negli adulti e può diminuire fino al 50% nei pazienti anziani. La cinetica della melatonina è lineare nel range 2-8 mg. La biodisponibilità è nell'ordine del 15%. Vi è un significativo effetto di primo passaggio con un metabolismo di "primo passaggio" stimato nell'ordine del 85%. La  $T_{max}$  si raggiunge dopo 3 ore in stato di nutrizione. La velocità dell'assorbimento della melatonina e la  $C_{max}$  dopo la somministrazione orale di Circadin 2 mg sono influenzate dal cibo. La presenza di cibo ha ritardato l'assorbimento della melatonina con conseguente ritardo ( $T_{max} = 3,0$  h vs.  $T_{max} = 0,75$  h) e diminuzione della massima concentrazione plasmatica in stato di nutrizione ( $C_{max} = 1020$  pg/ml vs.  $C_{max} = 1176$  pg/ml).

### Distribuzione

*In vitro* il legame della melatonina con le proteine plasmatiche è circa del 60%. Circadin si lega principalmente all'albumina, alla glicoproteina alfa<sub>2</sub>-acida ed alle lipoproteine ad alta densità.

### Biotrasformazione

Dati sperimentali suggeriscono che nel metabolismo della melatonina sono coinvolti gli isoenzimi CYP1A1, CYP1A2 e forse anche CYP2C19 del sistema del citocromo P450. Il metabolita principale è 6-sulfatossi melatonina (6-S-MT), che è inattiva. La biotrasformazione avviene nel fegato. L'eliminazione del metabolita si completa entro 12 ore dall'ingestione.

### Eliminazione

L'emivita terminale ( $t_{1/2}$ ) è di 3,5-4 ore. L'eliminazione avviene per escrezione renale dei metaboliti.

L'89% viene eliminato sotto forma di coniugati glucuronidi e solfati di 6-idrossimelatonina ed il 2% come melatonina (principio attivo immodificato).

### Sesso

È evidente un aumento della  $C_{max}$  di 3-4 volte per le donne rispetto agli uomini. È stata osservata anche una variabilità di 5 volte della  $C_{max}$  tra soggetti diversi dello stesso sesso. Tuttavia non è stata riscontrata alcuna differenza farmacodinamica tra uomini e donne nonostante le differenze nei livelli ematici.

### Popolazioni speciali

#### Anziani

È noto che il metabolismo della melatonina diminuisce con l'avanzare dell'età. Con vari dosaggi sono stati segnalati livelli maggiori nell'AUC e nel  $C_{max}$  in pazienti più anziani rispetto ai più giovani, a conferma di un minore metabolismo della melatonina nei soggetti anziani. I livelli della  $C_{max}$  erano intorno a 500 pg/ml negli adulti (18-45 anni) rispetto a 1200 pg/ml negli anziani (55-69 anni); i livelli dell'AUC erano di circa 3000 pg\*h/mL negli adulti contro 5000 pg\*h/mL negli anziani.

#### Compromissione renale

I dati dell'azienda indicano che non si verifica accumulo di melatonina dopo somministrazioni ripetute. Tale osservazione è compatibile con la breve emivita della melatonina nell'uomo. I livelli riscontrati nel sangue dei pazienti alle ore 23:00 (2 ore dopo la somministrazione), dopo 1 e 3 settimane di somministrazione quotidiana, sono stati rispettivamente di  $411,4 \pm 56,5$  e  $432,00 \pm 83,2$  pg/ml e sono simili a quelli riscontrati in volontari sani dopo la somministrazione di una dose singola di Circadin 2 mg.

#### Compromissione epatica

Il fegato rappresenta la sede principale del metabolismo della melatonina e di conseguenza l'insufficienza epatica si traduce in livelli più elevati di melatonina endogena. I livelli plasmatici di melatonina in pazienti con cirrosi sono risultati significativamente aumentati durante le ore diurne. I pazienti hanno presentato un'eliminazione totale di 6-sulfatossimelatonina significativamente ridotta rispetto ai controlli.

## 5.3 Dati preclinici di sicurezza

I dati preclinici non rivelano rischi particolari per l'uomo sulla base di studi conven-

zionali di *safety pharmacology*, tossicità a dosi ripetute, genotossicità, potenziale cancerogeno, tossicità della riproduzione e dello sviluppo. Negli studi preclinici sono stati osservati effetti soltanto ad esposizioni considerate sufficientemente superiori alla massima esposizione nell'uomo, il che indica una scarsa rilevanza clinica. Lo studio sul potenziale cancerogeno condotto sui ratti non ha rilevato alcun effetto significativo per l'uomo. In studi di tossicità riproduttiva, la somministrazione orale di melatonina a femmine gravide di topo, ratto o coniglio non si è tradotta in alcun evento avverso sulla prole, misurato in termini di vitalità del feto, anomalie scheletriche o organiche, rapporto numerico dei sessi, peso alla nascita e successivo sviluppo fisico, funzionale e sessuale. Un lieve effetto sulla crescita post-natale e sulla vitalità è stato riscontrato soltanto in ratti trattati con dosaggi molto elevati, pari ad un dosaggio di circa 2000 mg/die nell'uomo.

## 6. INFORMAZIONI FARMACEUTICHE

### 6.1 Elenco degli eccipienti

Ammonio metacrilato copolimero tipo B; Calcio idrogenofosfato biidrato; Lattosio monoidrato; Silice colloidale anidra; Talco; Magnesio stearato.

### 6.2 Incompatibilità

Non pertinente.

### 6.3 Periodo di validità

3 anni.

### 6.4 Precauzioni particolari per la conservazione

Non conservare a temperatura superiore a 25°C. Conservare nella confezione originale per proteggere il medicinale dalla luce.

### 6.5 Natura e contenuto del contenitore

Le compresse sono confezionate in blister strip di PVC/PVDC opaco con retro in foglio di alluminio. La confezione consiste in un blister strip contenente 7, 20 o 21 compresse, oppure in due blister strip contenenti 15 compresse ciascuno (30 compresse). I blister sono confezionati in astucci di cartone. È possibile che non tutte le confezioni siano commercializzate.

### 6.6 Precauzioni particolari per lo smaltimento

Nessuna istruzione particolare per lo smaltimento. Il medicinale non utilizzato ed i rifiuti derivanti da tale medicinale devono essere smaltiti in conformità alla normativa locale vigente.

## 7. TITOLARE DELL'AUTORIZZAZIONE ALL'IMMISSIONE IN COMMERCIO

RAD Neurim Pharmaceuticals EEC SARL

4 rue de Marivaux 75002 Paris Francia - e-mail: regulatory@neurim.com

## 8. NUMERO(I) DELL'AUTORIZZAZIONE ALL'IMMISSIONE IN COMMERCIO

EU/1/07/392/001; EU/1/07/392/002; EU/1/07/392/003; EU/1/07/392/004

## 9. DATA DELLA PRIMA AUTORIZZAZIONE/RINNOVO DELL'AUTORIZZAZIONE

Data della prima autorizzazione: 29 giugno 2007

Data del rinnovo più recente: 20 aprile 2012

## 10. DATA DI REVISIONE DEL TESTO

29 Marzo 2019

Circadin 2mg compresse a rilascio prolungato 21 cpr - Classe C - RR- Prezzo al pubblico € 21.90

Circadin 2mg compresse a rilascio prolungato 30 cpr - Classe C - RR- Prezzo al pubblico € 29.90

Informazioni più dettagliate su questo medicinale sono disponibili sul sito web della Agenzia europea dei medicinali <http://www.ema.europa.eu>.



## e riprendi il giusto ritmo.

Circadin® è indicato come monoterapia **per il trattamento** a breve termine **dell'insonnia** primaria caratterizzata da una qualità del sonno scadente in pazienti da 55 anni di età.<sup>1</sup>

Approvato  
**PER 3 MESI**  
di trattamento<sup>1</sup>

NUOVA  
CONFEZIONE  
**30**  
compresse<sup>1</sup>

Farmaco di Fascia C - RR, € 29,90

1. Circadin®. Riassunto delle Caratteristiche del Prodotto.  
Cod. 99000910 - Dep. Aifa in data 26/07/2019

