“The menopause is probably the least glamorous topic imaginable; and this is interesting, because it is one of the very few topics to which cling some shreds and remnants of taboo. A serious mention of menopause is usually met with uneasy silence; a sneering reference to it is usually met with relieved sniggers. Both the silence and the sniggering are pretty sure indications of taboo”

Ursula K. Le Guin [American Author]
A HISTORY OF THE MENOPAUSE

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Preface

This monograph on the history of the menopause is a by-product of the various influences in my postgraduate Obstetric and Gynaecological training. As Professor Mark Paul Brincat returned to our shores an increased interest in Gynaecological Endocrinology ensued. In conjunction with the ageing population, the menopausal aspect of Gynaecological Endocrinology came into sharper focus resulting in industrious scientific study of postmenopausal conditions in particular osteoporosis and cardiovascular disease.

As in any scientific venture, the historical milieu of medical endeavour is intriguing and sheds light for further scientific study. As another by-product of my postgraduate training, the medico-historical background of Professor Charles Savona Ventura imbued an avid interest in the historical setting of the menopause.

This monograph is thus the result of a sturdy alloy, amalgamating the science and history of the menopause. For this and more I am deeply indebted to both Professors Brincat and Savona Ventura.
Foreword

The 83-year-old American author Ursula Kroeber Le Guin wrote that “The menopause is probably the least glamorous topic imaginable; and this is interesting, because it is one of the very few topics to which cling some shreds and remnants of taboo. A serious mention of menopause is usually met with uneasy silence; a sneering reference to it is usually met with relieved sniggers. Both the silence and the sniggering are pretty sure indications of taboo”.

The Department of Obstetrics and Gynaecology of the University of Malta Medical School has definitely not subscribed to the above outlook towards the menopause. Since the 1990s, under the direction of Prof. M.P. Brincat, a team of researchers have led a series of research projects dealing with the menopause and menopausal complications. These studies, published and presented in the international fora over the last three decades, have placed the management of the menopausal woman in Malta at the forefront.
The attention to this subspecialty was not simply directed at academic research, but has filtered down to clinical practice making available front-line facilities for the management of Maltese menopausal woman. This has really been a case of translating research into patient benefits.

The Academic Department of Obstetrics & Gynaecology fully supports these endeavours and is proud of the achievements attained by this team.

Prof. C. Savona-Ventura
Head: Department of Obstetrics & Gynaecology
1 Introduction

The menopause has not attracted much medical attention throughout the ages until the latter part of this century. During the last forty years the slow trickle of medical interest has turned into a veritable flood to the extent that a significant proportion of gynaecological endocrinological research has been directed towards the menopause.

As in most of man’s endeavours, necessity is a powerful driving force and work on the menopause has taken a similar course. Most of the early medical writings concentrated on the onset and mean age of the menopause possibly due to the related sexual and subfertile inconvenience.

As early as the 4th century B.C., Aristotle had indicated that the
mean age of the menopause was around 50 years (Fig 1.). In his work *Historium Animalum*, Aristotle writes about the menopause, “As for their end, the menstrual discharges ceases in most women about their fortieth year; but with those in whom it goes on longer it lasts even to the fiftieth year, and women of that age have been known to bear children. But beyond that age there is no case on record”. Aristotle also refers to symptoms of the climacteric, “with this qualification that there is a lack of fertility at the commencement of these symptoms, and again towards their close when the emissions become scanty and weak”. ¹

The age of menopause in women was further confirmed by classical physicians such as Pliny the Elder and Soranus the Greek gynaecologist from Ephesus. The latter commented that “...it finally comes to an end, usually not earlier than forty, nor later than fifty years. Now again

“usually” has been added, for in some women menstruation continues till sixty”.2

In the sixth century A.D., the Greek Byzantine Physician, Paulus Aegineta (Fig. 3) stated “The menses cease about the fiftieth year of age, a few have them until sixty, and with some they begin to disappear about thirty-five, particularly with such as are fat”. Possibly the latter obese women were actually suffering from polycystic ovarian syndrome. In the sixth to seventh centuries AD, Paulus Aegineta wrote a comprehensive medical Compendium of Seven Books Epitomes iatrikes biblio hepta which dealt with osteoporosis as it affected the hip and the vertebrae separately. He wrote that the stimuli

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2 books.google.com.mt/books?id=YsKWfh31gxwC&printsec=frontcover&dq=Soranus&hl=en&sa=X&ei=DvTST6H1MK3P4QSoxJWzAw&ved=0CDIQ6AEwAA#v=onepage&q=Soranus&f=false pg.17. See also Pliny the Elder [Historia naturalis 7.14.61] and Saint Jerome who states that the postmenopausal woman “ceases to be a woman and is freed from the curse of God” [Adversus Helvidium 20].
were sometimes physical while sometimes "sorrow, care, watchfulness and the other passions of the mind can excite an attack of the disorder (or menopausal symptoms)".  

In the eleventh century in her medical book entitled (Causae et curae (Causes and Cures, 1150), Hildegard of Bingen indicated that “the menses ceases from the fiftieth year and sometimes in certain ones in the sixtieth when the uterus begins to be enfolded and contract so that they are no longer able to conceive” (Fig. 4).

In his encyclopaedic work De Natura Renum, Thomas of Cantimpré (13th century A.D.) declared that “a woman

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3 books.google.com.mt/books?id=AFdhAAAAIAAJ&q=women#v=snippet&q=women&f=false see pg.608
conceives up to the fiftieth year. Gilbertus Anglicus in his work *Compendium Medicinae* writes that “The menses are naturally withheld below twelve and fifty years”. In *De Renum Proprietatibus* written by Barthlomaeus Anglicus stated “The menses naturally was to be a matter of generally occur between the fourtieth and fiftieth year”. In the thirteenth century Lily of Medicine (*Lilium Medicinae*) by Bernard de Gordon wrote that the normal ages of menstruation was between fourteenth and fiftieth year. Another literary work given a flowery name, the Rose of Medicine (*Rosa Medicinae*) by John of Gaddesden asserted “The menses are naturally withheld between the ages of twelve and fourteen till the age of fifty”.

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Evolution and the Age of the Menopause in Humans

Menopause is a puzzling evolutionary aspect of human biological history. *Prima facie*, termination or indeed an early end of the reproductive process goes against the grain of Darwinian natural selection.

An intriguing hypothesis as to determination of the average age of the menopause has been suggested by some biological anthropologists.\(^5\) It is thought that the mean age of the menopause was determined by the crude laws of “survival of the fittest” early on in man’s evolution.

It is obvious that females of the hominid race who developed a premature menopause were disadvantaged by the inherent lack of fertility to provide sufficient offspring for the continued survival of their subspecies. However other variables are thought to have been at work eventually leading to the “final” adjustment of the average age of the menopause to around 50 years.

\(^5\) Amundsen DW, Diers CJ. The age of the Menopause in Medieval Europe. *Human Biology* 1973, 45:605
Three basic differences between the human race and other species are thought to have had a bearing on establishing the age of reproductive senescence. The burden of gestation, parturition and lactation together with their attendant complications encouraged a significant reduction in litter and family size. As opposed to other species the evolution of the hominid race was accompanied by an exponential increase in encephalization and development of the intellect. This led to a lengthening of the period of the juvenile dependence which is the longest of all the animal species.

All these three factors encouraged the situation where mothers with relatively small families were more likely to survive and adequately care for their offspring. Conversely mothers with “excessive fertility” were inevitably unable to provide adequate care for their young predisposing to greater risk of childhood mortality. Moreover the resultant “familial overpopulation” further drained the limited environmental resources available to a hunter-gatherer community. These adverse conditions may have led to the elimination of the “excessively fertile” subspecies. On the other hand, the relatively subfertile subspecies survived the 50-year mark for the onset of the climacteric and menopause seems to have been established some 1.5 million years ago, and it
appears that it is this subspecies which has survived to the present day.\textsuperscript{6}

Evolutionary pressures may not only be due the extreme altricialty of human offspring. The progressive difficulty of delivering babies with relatively large brains increased the risk of childbirth not only to the foetus but also to the mother. In conjunction with increased risk of childbirth due to the enlarged foetal brain, elevated maternal age is associated with adverse outcomes in both pregnancy and labour. Moreover the elderly mother is likely to have existing offspring who due to inherent human altriciality depend on her. There may be little advantage from the evolutionary point of view for the older mother in running the increased risk of further pregnancies.

An alternative theory is that within the extended family groups, natural selection prevailed through the development of the menopause. This occurred because by producing post-reproductive grandmothers, the family group increased the survival not only of existing offspring but also those of their adult daughters.

Taking into consideration the circumstances of relatively high background mortality typical of ancestral environments the

\textsuperscript{6} Peccei J.S. Menopause: Adaptation or Epiphenomenon. Evolutionary Anthropology 2001, 10:43–57
individual hypotheses for the establishment of the human menopause, fail the test of natural selection. However a combined approach incorporating all the above hypotheses can explain why menopause may have evolved. From the physiological point of view, the establishment of the human menopause, is such a significant event in human biological history that it is likely that several factors came into play so as to fit into the process of natural selection.7

3
The social impact of the Menopause

The biological establishment of the average age of menopause at around 50 years had two significant socio-anthropological implications, which to a large extent have also influenced subsequent medical interest and research in the menopause. Firstly, for most of man’s existence, two million years excluding the latter half of this century, the menopause occurred relatively late in the average human lifespan.

CLASSICAL PERIOD: In ancient Egypt the onset of the menopause in a woman may have been considered as the onset of female ageing. This was undoubtedly due to the fact that childbearing was considered as
the primary role of women in Ancient Egyptian society besides other menial jobs. This attitude did not apply to women of noble descent whereby their social status appeared to protect them from the effects of the menopause and the ageing process.

However there is little evidence in Ancient Egyptian text regarding the menopause possibly due to the fact that most literature then was written by and concerned men. Moreover the relevance of the ageing process was given importance mainly to male section of society rather than to females.

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9 Freed, R., Markowitz, Y.J., d’Auria, S. *Pharaohs of the Sun*, Boston, 1999
The male dominance in Egyptian literature on the ageing process displays itself when the elderly vizier Ptahhotep in an emotional entreaty to Pharoah to retire in favour of his son, describes the experience of ageing in a literary text from the beginning of the 2nd millennium BC:

*Senescence has come, elderiness descended.*
*Weakness has arrived, helplessness returns.*
*As one spends every night becoming more childish.*
*Eyesight has diminished, the ears become deaf.*
*Strength is perishing from my heart’s fatigue.*
*The mouth has fallen silent and cannot speak.*
*The heart is exhausted and fails to remember yesterday.*
*Bones ache because of length (of years).*
*Good has become evil.*
*All taste is gone.*
*What old age does to people*
*Is evil in every respect*
*The nose is blocked and cannot breathe*
*from weakness in standing and sitting.*

The medical papyrus *Ebers* contains a paragraph referring to a woman who was amenorrhoeic for many years. The amenorrhoea was accompanied by a burning sensation in the stomach which was only relieved by vomiting clear fluid. This instance may have
attracted medical attention as initially the elderly woman may have been thought to be pregnant and developed hyperemesis gravidarum. In the face of the inexplicable absence of pregnancy the diagnosis declared in the *Ebers* papyrus is that the woman was bewitched. This may have been one of the first literary references which connected witchcraft and the menopause, a linkage that was consolidated in the middle-ages.

During the reign of Rameses II, the awareness that postmenopausal women were infertile was certainly common knowledge. At around 1250 BC Hattusilis III, king of the Hittites, requested Rameses II to send a doctor to prepare a fertility medicine for his sister. Although Rameses II agreed to send one of his physicians, he indicated that the cause of Hattusili III sister’s infertility was more likely her age. There is a suggestion that Rameses II actually replied in a rather ungallant manner that at the age of sixty Hattusili III’s sister was beyond hope. This Rameses II did, twenty years after the famous Battle of Kadesh between the Hittite and Egyptian Kingdoms sealing the first written peace treaty.¹⁰

In Roman times the average life-expectancy was only 25 years. More serious life-threatening conditions such as infectious epidemics and the disastrous effects of famine dictated the

attention of the few with a medical interest. The Greek physicians such as Aristotle and Hippocrates gave scanty mention of the diminished sexual powers after the menopause.

**MEDIEVAL & RENAISSANCE PERIOD:** The limited life-span in Medieval times and the Renaissance again left a similar negative influence on medical interest in the menopause.

A second more subtle disadvantage of the climacteric is its effect on sexuality in particular the “social and species” inconvenience as regards succession. The importance of leaving an heir has been of paramount importance through most of man’s existence. The importance of succession may have been exacerbated by the insecurity induced by the short life-span compared to the present day. Moreover despite all religious conviction immortality may have been achieved indirectly, by having offspring with a similar genetic make-up.

These influences may be appreciated by the exaggerated personal failure of several renowned personages in history who failed to obtain an heir. Following the ruinous civil War of the Roses, successfully terminated by his father Henry Tudor, King Henry VIII wanted a male heir to consolidate the power of the Tudor dynasty. King Henry VIII went to great lengths of having six wives and in the process beheading three of them in a vain effort to obtain a suitable male heir. The fates of the wives can be
The inability to have an heir to the French throne by Napoleon I was cause for great derision by some of his contemporary European monarchs. Napoleon knew that although his wife Josephine had proven fertility at an earlier date by the birth of two children by her first husband, she was unable to produce an heir for Napoleon. The cause of her infertility could have been the onset of the climacteric or even menopause by that time.

In desperation, Napoleon undertook several sexual liaisons while carrying out his European-wide campaign. Following his victory at the Battle of Austerlitz, also known as the battle of the Three Emperors 1805, an elated Napoleon had an affair with a Polish noble woman Countess Marie Walewska. The affair was encouraged by Polish nobility in an effort to gain Polish independence from the Russian and the Austro-Hungarian Empires.

Following the liaison with Napoleon, Countess Marie Walewska became pregnant. In the eyes of Napoleon this confirmed that the fertility problem by that time was his wife’s Josephine. Napoleon went on to divorce Josephine and married Princess Marie Louise daughter of the Emperor of Austria. With Marie Louise, a son was remembered as "Divorced – beheaded – died – divorced – beheaded – survived."

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born (nominally enthroned as the Prince of Rome), but the son
died at a young age.

Conversely the absence of an heir to Julius Caesar and his wife
Calpurnia was not depicted as a weakness in the eyes of Classical
Roman society. Julius Caesar went on to “adopt” his nephew
Octavian. Possibly due to a certain element of meritocracy imbued
in Roman times, adoption on merit was an acceptable alternative
to the lack of a genetically connected heir.

However in other societies it was so important to produce an heir,
that the Bible reveals two instances where divine intervention is
said to have reversed the curse of menopausal infertility. The first
instance in the Old Testament, involved Abraham and his wife
Sarah who at the age of 90 years gave birth to Isaac. “Then God
said, “Yes, but your wife Sarah will bear you a son, and you will call
him Isaac”.

In the New Testament, the medical disciple Saint Luke describes a similar incident when the old ‘barren’ Elizabeth
bore a son named John, to the old Pharisee Zachariah “your prayer
has been heard. Your wife Elizabeth will bear you a son, and you
are to give him the name John. He will be a joy and delight to you,

York: Doubleday and Co. Publ, 1968;17:15-18
and many will rejoice because of his birth, for he will be great in the sight of the Lord” (vv. 13-15).

Despite the limited life-span, even in the middle ages some women did reach the menopause. These women mainly belonged to ducal families whereby in England, for example, a 20 year old lady of noble descent would be expected to live beyond the age of 50. A notable exception was the fourteenth century when the average life expectancy dropped to below forty-five years. The drop in life expectancy during the fourteenth century may have been due to the ruinous War of the Roses which mainly involved the noble families, leaving the common people relatively unscathed.

During the fourteenth century there also existed Julian of Norwich “the first English woman of letters” but also described as “more metaphysical than the other English mystics”. Julian of Norwich at the age of 50 became an anchoress, an occupation that allowed her to have time to read, pray and reflect. Norwich at the time was only second to London as regards wealth and population density. Moreover Julian of Norwich witnessed the ravages of the Hundred Years War, the Great Schism and the successive waves of

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havoc caused by the Black Death in 1348-1349, 1361-1362 and again in 1369. Local strife also prevailed with the crushing of the Peasants’ Revolt by the Norwich militaristic Bishop Despenser, John Wycliffe’s condemnation and the bishop’s siege of Ypres. All this discord brought unnatural poverty, premature death, demoralisation and depression amongst the populace. Written at around the age of 50 years, Julian of Norwich wrote her “Book on Showings” demonstrating a determined search of rational supports of hope. In the Book of Showings, Julian of Norwich depicts an intuitive sense of human nature towards a natural tendency towards good. Despite all the discord and strife that surrounded her, Julian of Norwich well beyond her menopause displayed a remarkable positive attitude to mould her epistemological optimism.\textsuperscript{14}

With the passage of time the average life expectancy increased and as a corollary more women reached the age of the menopause. Similar to medieval times, during the Renaissance, women of noble descent preceded the commoners. These women exerted political and economic pressures so that their physicians would intervene in an effort to attenuate the bothersome symptoms of the climacteric.

During the Renaissance, the renewed intellectual, political, and artistic development, the “rebirth” of civilization benefited mainly men. The speed this development necessitated to compensate for the time lost during the Dark Ages and its convenience favoured the male portion of Renaissance society. Following the termination of the Hundred Years War (1337-1453) between France and England, then followed the War of the Roses (1455-1485) whereby English noblemen and European mercenaries fought on English soil, allowing relative peace on the European continent.

Instead of engaging in warfare, men in Europe were able to direct their attention towards political, academic and artistic development. This involved the recouping of the classical writings of the ancient Greeks and Romans. The fall of the Byzantine Empire led to the migration of Greek scholars to Europe in particular the Italian peninsula. The Italian Renaissance, the beginnings of the European Renaissance, was influenced by the scholarly and scientific writings of the ancient sages, like Aristotle and Hippocrates. Moreover medieval notions prevailed, whereby women were depicted as being either good, submissive, and chaste, the reference point being the Virgin Mary; or evil, active, and promiscuous referring to Eve.¹⁵

¹⁵ Kelly-Gadol J. “Did Women have a Renaissance” Women, History and Theory. University of Chicago Press 1986
The artists of Renaissance Italy, such as Leonardo Da Vinci, Michelangelo Buonarotti, and Botticelli see the women of this time as important for perpetuating family lines. Da Vinci’s Mona Lisa is a fine example of a woman at the peak of her reproductive life. The vulnerability implied by the reproductive function of the Renaissance woman may have been further accentuated by Titian’s colourful “Rape of Europa”. Similarly the architects of the time such as Brunelleschi, Alberti and Bramante again depict women in the prime of their life and eschew from including any statues demonstrating the postmenopausal women. Alberti went on to write “I Libri della Famiglia” further
extolling the domestication of Renaissance women. It is suggested that Alberti’s opinions on the role of women in society were formulated by Xenophon’s treatise, “Oeconomicus” (circa 362 B.C.). Undoubtedly the subject and nature of these Italian works were directed by the needs of their male patrons whose main preoccupation with the role of women in Renaissance Italy was for helping men in their endeavours and to keep their male companions comfortable and content.

There were few wealthy noble women who held some power and influence during the Renaissance. However, most menopausal women from the upper social class had very limited roles in society. As in ancient times, legitimacy of heirs was of paramount importance further decreasing the relevance of the menopausal woman in Renaissance society. As a demonstration of their husbands’ or fathers’ social status, wives and daughters were expected to be charming and dressed elaborately. Daughters could be utilized to enter alliances with wealthy and powerful families.

The rigid patriarchal social structure possibly under the influence of the Protestant and later Catholic Reformations led to expressions of misogynistic violence mainly directed towards menopausal women. The ruinous Thirty Years War (1618-1648) fuelled religious strife in Central Europe. The fear of change and the loss of security augmented the anxiety of the period, which
resulted in the largest executions of women known to European history involving the witch-hunts of the sixteenth century. During the period of 1560 to 1670, these executions led to the killing of probably 30,000 or more women. Women accused of being witches tended to be women outside male control. Accused witches were overwhelmingly women past the menopause who lived alone on the outskirts of rural settlements.  

**THE ENLIGHTENMENT:** Following the Renaissance, the Age of Enlightenment on the European Continent followed. The advances in science were directed to various and diverse spheres of human activity such as warfare and medicine. The French Revolution and the subsequent Napoleonic Wars changed the political face and thinking of Europe.

The life expectancy of women of the Ancien Regime and the new Napoleonic elite had increased so that the proportion of women entering the menopause amplified itself. With the loss of their husbands due to civil strife and warfare came the loss of possessions, property and the livelihood of their young threatened.

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The French were always considered more concupiscent by most of their European neighbours. Moreover sexual licence in France followed the Reign of Terror and this provided some form of emotional and sexual security to young French women. Menopausal women from both the Ancien Regime and the Napoleonic elite risked missing on this opportunity. As a reaction women in the climacteric or menopause flocked in their thousands to French physicians for relief of their symptoms.

Following the Napoleonic Wars, during the late seventeenth century, significant social changes were occurring in Europe which were to have an impact on most aspects of life including the health of the general population. Political stability encouraged rapid economic growth. The average life-expectancy rose due to the improved agricultural systems and the virtual disappearance of the plagues.

With the rise in the expectation of life in Europe the problems associated with the menopause became more evident. In France, similar to the early post-Napoleonic era, the sexual needs of the female bourgeoisie and royalty induced these women to flock to their sympathetic physicians. A French physician called Longrois once wrote about the menopause “the maxim that nature is the best healer of women in the climacteric, as indeed any ailing woman at any time, is as false as it is heartless. Nature can heal only simple ills, due to fortuitous physical causes. Women’s
maladies are always complex affected by their sensitivity and their mental state”.

Besides the irksome symptoms such as hot flushes and night sweats, vaginal atrophy exacerbated sexual dysfunction thwarting many an amorous design. Thus during the period of the enlightenment, women turned to male doctors not only for aid during childbirth but for other ills including the climacteric. The last taboos preventing male physicians from sharing an interest in the menopause were swept aside. ‘Inside information’ regarding menopausal symptoms became common knowledge making them more amenable to treatment.

So desperate were some French women that some were able to tolerate the most bizarre of treatments. Physicians such as Brounnaïs would use emmenagogues, bleed, leach and purge their female clients in an effort to appease the climacteric symptoms of their patients. Some were considered ‘successful’ if by coincidence the definite menopause occurred soon after the treatments. Most were not so fortunate.

On the West side of the English Channel, the number of perimenopausal women similarly increased during the Victorian era, since the average life expectancy of the population had well

exceeded forty years. However British women received a completely different attitude from their local physicians. This may have been induced by the influence of Ascepleadean solidism replacing thinking based on Hippocratic humoralism. This put the understanding of the climacteric and the menopause (very much humoral influenced) at a major disadvantage. In fact, Fothergill upheld that since nature was the cure for most ills, the menopause being a natural ill was best treated conservatively. Conservatism was supported most vehemently by some English clinicians whereby they derided doctors treating climacteric symptoms insinuating that the menopause may even be considered an iatrogenic disease. Other physicians were more congenial as may be implied from anonymous English publication in 1727. ‘A Physician’ interestingly suggested the use of ‘uterine drops’ to cure certain ills associated with the menopause.

THE 19TH CENTURY: In 1816, Gardanne first coined the work *menespausie* and later shortened it to menopause. This reflects

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18 Simson T. *The system of the womb with particular account of the Menses Independent of a Plethora; to which are subjoined a few observations relating to the menopause and its effects upon the body*. Edinburgh: R Fleming & Co. 1729.


20 A Physician (anonymous). *The Ladies’ Physical directory or a Treatise of all the weaknesses. Indispositions and diseases peculiar to the female sex from eleven years of age to fifty or upwards*. 1739:21.

21 Gardanne C. *Avis aux femmes qui Entrant dans l’age Critique*. Paris: Gabon 1816:Ch 6
the major advances and research on the menopause carried out in eighteenth century France. More than thirty theses on the climacteric and the menopause were presented at French Universities. Again physicians in both the United Kingdom and Northern America lacked enthusiasm towards research and treatment of the climacteric. Outside France doctors showing an interest in the menopause were looked upon with suspicion. Only one book concerning the menopause was published in English. This was undertaken by Tilt in 1857 and yet this was not well received.  

Despite much resistance to medical advances in the menopause some isolated interesting observations were done by some physicians in the latter part of the nineteenth century. Bruns in 1882 noted that more menopausal women had more fractures than men of the same age. This was surprising since more men were exposed to occupational hazards conducive to trauma. In 1896, Emil Knauer demonstrated that castrated animals developed sexual characteristics when the ovaries were transplanted into their bodies. Three years later, Williams in his book “The Influence of Sex in Disease” intimated that conditions

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22 Tilt ES. The Change of life in Health and Disease; A Practical treatise on the nervous and other effectations Incidental to women at the decline of life. 2nd Edition. 1857:97-107.

associated with the ageing process appeared to be accelerated with the onset of the climacteric and the menopause.\textsuperscript{24}

Similar allusions to the exacerbation of cardiovascular disease after the menopause were made during the latter years of the eighteenth century. “Hardening of the arteries” had been suggested to occur after the menopause. Cessation of menses was thought to be due to the ageing effect of the menopause on the uterine arteries.\textsuperscript{25} Since the 1800’s, the oestrogens have been known to modulate vascular tone and vascular reactivity. In 1884, MacKenzie reported that the menstrual cycle and pregnancy could cause changes in degrees of hyperaemia and vascularity in the mucous membranes of women. Sixty years later, Reynolds and Foster noted that oestrogens induced dilatation of small vessels in the ears of ovariectomised rabbits.\textsuperscript{26}

Even as regards males, hormonal deficiency was implicated in the debilitating effects of the ageing process. To this end, attempts were made to reverse the effects of the ageing process by the administration of testes extract. In 1889, the famous physiologist Charles Brown Sequard announced to the ‘Societe de Biologie’ in Paris that he had succeeded in reversing his physical decline due

\textsuperscript{24} Williams R. \textit{The influence of sex in disease}. London: Churchill, 1885.
\textsuperscript{25} Leake J. \textit{Chronic or slow disease peculiar to women}. London: Baldwin 1777.
\textsuperscript{26} MacKenzie J. Irritation of the sexual apparatus. \textit{Am J Med} 1884;87:360-5; Reynolds S, Foster F. Peripheral vascular action of oestrogen observed in ears of rabbit. \textit{J Pharmacol Exp Ther} 1940;68:173-7.
to ageing, by injecting testes extract. For centuries, it was believed that testes extracts possessed aphrodisiac and rejuvenating properties. Both the Greeks and the Romans utilised it for these reasons. The emperor Caligula, is said to have swallowed extracts of wolf testes during his dietary debauches. This myth continued until the early 20th century when some surgeons went to the extent of offering to rejuvenate old men by transplanting goat testes into their scrotum. Although there was wide ranging support for gland grafting among the medical profession, this was all based on anecdotal claims of success. In the late 1920’s, an English surgeon Mr. Kenneth Walker alluded to his own limited success with testes transplants and later on went on to say that the gland grafts were ‘no better than the methods of witches and magicians’.

THE 20th CENTURY: The discovery of insulin in 1921 heralded a new era in endocrinology. Two years later oestrogen was discovered in high quantities in ovarian follicular fluid. Oestrone was isolated in 1929. Soon after hormone assays became possible and this was followed by the development of the first oestrogen like compound which was called stilboestriol. Albright in 1940 was the first to link osteoporosis to ovarian failure in women when he noted that 40 out of 42 osteoporotic patients were women and all these women had passed the menopause. Albright et al were thus

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28 Hamilton D. *The monkey gland affair*. 1927, p.135
the first to coin the condition postmenopausal osteoporosis and a year later, a medical publication on postmenopausal osteoporosis by the same authors appeared in the Journal of the American Medical Association.\textsuperscript{29} Since then, much work was carried out on the initial premise laid out in this publication. Following this deduction it was noted that the removal of functioning ovaries from women below the age of 45 years, accelerated bone loss. The degree of bone loss depended on the time that elapsed since oophorectomy or spontaneous menopause.\textsuperscript{30} Moreover severe osteoporosis was noted in young women with congenital gonadal dysgenesis.\textsuperscript{31}

The association between cardiovascular diseases soon followed suit. Throughout the Framingham study initiated in 1948, a significant rise in ischaemic heart disease was noted after the menopause. In this study no premenopausal women were found to suffer from coronary heart disease. Ten years later two studies carried out in Edinburgh indicated that both a premature

\textsuperscript{29} Albright F, Smith PH, Richardson AM. Postmenopausal osteoporosis - its clinical features. \textit{JAMA} 1941;116:2465-2474


\textsuperscript{31} Brow D, Jowsey J, Bradford D. Osteoporosis in ovarian dysgenesis. \textit{J Pediatr} 1974;84:816
menopause and bilateral salpingo-oophorectomy were associated with an increased incidence of ischaemic heart disease.\textsuperscript{32}

Two population studies in 1978, one held in Goteburg\textsuperscript{33} and the other a continuation of the Framingham Study, indicated that cardiovascular disease was commoner in women who experienced an earlier menopause.\textsuperscript{34} Rosenberg et al confirmed the increased incidence of cardiovascular disease after the menopause and also showed that women who had undergone a surgical menopause before the age of 35 were seven times at greater risk of myocardial infarction compared to premenopausal women of the same age.\textsuperscript{35}

The next step involved direct studies between hormone replacement therapy and the prevention of cardiovascular disease.

\textsuperscript{32} Oliver MF, Boyd GS. Effect of bilateral ovariectomy on coronary artery disease and serum lipid levels. Lancet 1959;i:690-94; Sznajderman M, Oliver MF. Spontaneous premature menopause, ischaemic heart-disease and serum lipids. Lancet, 1963;i:962-5
in postmenopausal women. Several case-control studies\textsuperscript{36} and later cohort studies were carried out in the latter two decades of the 20\textsuperscript{th} century and in the main most revealed a lower relative risk ratio for cardiovascular disease in women taken hormone replacement therapy.\textsuperscript{37} This applied for both myocardial infarction and cerebrovascular accidents.

The 1990’s prospective randomised control trials however showed different trends. Initially the Heart and Estrogen/progestin Replacement Study (HERS) trial conjugated oestrogens in the treated group showed a null effect on the incidence of cardiovascular disease.\textsuperscript{38} After the HERS trial the larger Women’s Health Initiative (WHI) followed indicating that in the older cohorts of postmenopausal women there was a greater incidence...


of breast cancer and cardiovascular disease in the conjugated oestrogen treated groups.\textsuperscript{39} Both the HERS and WHI studies had the inherent disadvantage that hormone replacement therapy was on average administered to older women well past the menopause. It is of significance that the average age of treatment in the WHI study was 64.9 years, an age where in practice hormone replacement therapy is rarely administered for the first time. The age factor has drawn much criticism as younger cohorts in the WHI study did not reveal increased cardiovascular incidents and also demonstrated a lower all cause mortality.

At the turn of the 21\textsuperscript{st} century, more recent studies where hormone replacement therapy in the form of oestradiol administered to younger menopausal women have revealed lower all cause mortality and lower cardiovascular and breast cancer incidents. The Danish Osteoporosis Prevention Study and the Kronos Early Estrogen Prevention Study (KEEPS) did not show a rise in myocardial infarction and cerebrovascular disease in the hormone treated groups.\textsuperscript{40} Moreover the breast cancer rates did


not differ between oestradiol treated and control groups. It appears that at this point in time the perimenopausal period provides a window of opportunity whereby symptomatic women can be prescribed hormone replacement therapy safely in the short-term for symptomatic relief and possibly lower risk of all-cause mortality without excess in cardiovascular disease and breast cancer.

CONCLUSION: Towards the mid-twentieth century, Robert Wilson bravely published “feminine forever”. Wilson exhorted that hormone replacement therapy should be prescribed for life indeed to quote “to the grave”. He maintained a strong conviction that hormone replacement therapy could curtail the deleterious effects of the menopause. This radical view towards the menopause and its treatment attracted much criticism from the medical community of the time. Fortunately some clinicians did support Wilson one of these being Robert Greenblatt. Greenblatt’s understanding of the menopause typifies the perspective that is slowly being accepted by most specialists in gynaecological endocrinology nowadays. This can be amply appreciated from one of Greenblatt’s statements regarding the menopause “a woman in the autumn of her life deserves an Indian summer rather than a winter of discontent”.

4
The Maltese perspective

Archaeological findings of osteoprotic bones in the Maltese Islands are hard to come by. Firstly the nature of the pathology of osteoporosis renders the affected bones to be unfavourable candidates for fossilisation. The loss of both connective tissue and bone mineral during the osteoporotic process does not provide appropriate “scaffolding” for calcium impregnation during the fossilisation process. However at St Gregory’s Church in Zejtun burial remains pre-dating the 15th Century have shown long bones thought to belong to a menopausal osteoporotic woman. Radiological examination of these bones reveal extreme translucency of elderly female bones suggesting postmenopausal osteoporosis. The paucity of osteoporotic archaeological finds is also due the fact that in the great majority of women the average life expectancy did not exceed the average menopausal age until the early 20th century.

Similar to other countries, Maltese medical interest in the menopause has only attracted significant interest over the past century. This interest was modulated by several factors including the average age of life expectancy, the rampant existence of
infectious diseases, the high perinatal and infant mortality rates and the widespread malnutrition pervading the islands. With the introduction of basic Public Health measures and the use of antibiotics the incidence of infectious diseases decreased significantly and perinatal and infant mortality rates improved substantially. Consequently the average life expectancy increased and surpassed the age of menopause with the result that the majority of 20th Century Maltese women would experience the menopause and its aftermath.

Late Medieval Skeletal Remains
St. Gregory Church, Zejtun, Malta

By 1937 local interest in the menopause is demonstrated by the management of surgical menopause performed on premenopausal women by Professor Guze Ellul. Following the auto-implantation pre-clinical experiments undertaken by Emil Knauer, Professor Ellul emulated this work by introducing the
premenopausal ovaries in the vulva. However by 1947 the practice of ovarian auto-innestation in the subcutaneous tissue fell out of favour.

Following the abandonment of ovarian auto-innestation, artificial application of oestrogen was administered in various forms. Symptoms of oestrogen deficiency were treated by hormonal preparations such as Aestroform which was administered by a hypodermic needle. In 1948 another preparation called Fertinets was available on the market and was advertised as “activated hormone preparations efficacious at combating the premature effects of advancing age and nervous debility”. This statement refers to activated hormone preparations presumably due to the widespread notion and possibly also experience that several household remedies to combat menopausal symptoms have been attempted without significant success. Also attractive is the reference to a possible elixir to address the unwanted effects of “advancing age” which is associated with symptoms overlapping with the menopause.42

The application of oestrogen to address the “nervous debility” associated with the menopause was Climatone (1954) which was described as “sedative-free control of menopausal disorders without side-effects”. This description demonstrates the perennial ambivalence both by the woman and medical profession in

42 Savona-Ventura C. History of gynaecology in Malta. UMMS, Malta, 2010.
treating menopausal disorders. On the one hand menopause is considered a natural phase in a woman’s life associated with the body’s natural reactions to a change in the hormonal milieu. The implication of this is that natural ills should be allowed to take their own course without medical intervention. On the other hand the menopausal symptoms may be quite bothersome impacting the woman’s quality of life demanding treating.

Two years later (1956) a product named Multigland was put on the market in Malta. This product was marketed as a treatment for “menorrhagia, hysteria, neuroasthenia and menopausal disorders”. Hormonal therapy is an effective treatment of menorrhagia due to perimenopausal dysfunctional bleeding. However until then the connection between the hormonal milieu and malignancy had not been confirmed. It was only in 1966 when Huggins and Rous were awarded the Nobel Prize for Physiology or Medicine that the influence of hormones on the onset and growth of certain forms of human cancer was determined. This work demonstrated that cancer cells are not necessarily autonomous and self-perpetuating and that some depend on chemical signals such as hormones to survive. This insight led to the development of anti-hormone such as tamoxifen and hormone therapy as a treatment for endocrine-dependent tumours.

In the 1960’s hormone therapy became more fashionable only to diminish a decade later. Oestrogen treatment was associated with
an increase in postmenopausal bleeding and it was advised that routine or prolonged use should be discouraged. This more so with a background population with elevated rates of high body mass index, diabetes and hypertension, all risk factors associated with endometrial carcinoma.\textsuperscript{43}

With lower doses combined with progestins renewed interest gained ground locally in the early nineties. This interest gained momentum as the impact of postmenopausal osteoporosis with high fracture rates increased with the expanding ageing population. Moreover the impetus for research in postmenopausal osteoporosis was stimulated by local workers who had undertaken significant strides in basic science research in the contribution of the connective tissue component to the development of osteoporosis.\textsuperscript{44} Local research initiated with establishing and publishing on incidences of postmenopausal osteoporotic fractures in the Maltese Islands. This work encouraged the investment in bone densitometry which further


aided research and further publication. Following work on bone densitometry other variables such as the intervertebral disc and femoral trochanteric cortical thickness was looked into and gained a more holistic perspective of postmenopausal osteoporosis.


Humanity’s interest in the menopause throughout the ages has waxed and waned mimicking the cyclical nature of hormonal physiology. The cyclical character of human interest may due to myriad factors such as the basic social conditions, affected by ever changing political landscape, the undulant gradient of human civilisation and the scientific milieu of the healthcare professionals. These factors will remain perennial throughout human existence and so will its interaction with the menopause.