C. ALLEGRA - P.L. ANTIGNANI - E. KALODIKI

NEWS IN PHLEBOLOGY

EDIZIONI MINERVA MEDICA

ISBN: 978-88-7711-778-6

Foreword

Dear Readers,

It was with great honor and pride that I received the assignment to write a few lines on this important scientific publication in the phlebology field.

Lately, we have been observing a quick development of new knowledge in phlebology.

In fact, many pathophysiology, anatomical, diagnosis and therapy principles have deeply improved in the past decades.

For many years the vascular surgeons preferred to dedicate to the arterial pathologies rather than to the venous disease, regarded as trivial.

But, the new technologies such as the ultrasound Doppler, laser, radiofrequency, foam sclerotherapy, the better quality of the elastic stockings and bandages associated to a reduction of invasive surgical procedures, increased the interest in the phlebology field.

Recently published papers showed a high incidence of the venous pathology as well as a great social economic burden. These findings also contributed to influence doctors' decisions and interest into phlebology.

This book aims to present the new findings on the venous disease. It includes chapters on new anatomical and physiological findings, along with new challenges of microcirculation and the genesis of the disease. It also describes new diagnosis and treatment methods which range from the traditional to the most modern. Finally, the great venous complex syndromes and coagulation disorders, such as thromboembolism, have been here discussed.

Therefore, this is an indispensable reference book also useful in phebology courses.

My congratulations to the authors for this great project and their hard work.

Angelo Scuderi
President of UIP

Preface

I was very glad when Pier Luigi Antignani, on behalf of the authors of "News in Phlebology", asked me to write the preface to this book.

Usually it is not easy to present the work of colleagues if you have been working with them for a long time and you share solid ties and mutual professional esteem.

However, in this case it is different, so it is easier to present a book that completes in such an exemplary way a scientific and training path that began many years ago.

The Italian College of Phlebology, of which I was appointed President this year, under the leadership of its founder Claudio Allegra began to focus on the scientific, social and cultural aspects of phlebology, centered on training and education.

"News in Phlebology" is, in this historical moment, the most comprehensive and updated text on training and information regarding venous and lymphatic diseases.The authors' vast experience and the ability of such an international and outstanding "parterre" to captivate the reader are the premise of a worldwide success.

Stefano de Franciscis
President of the Italian College of Phlebology

Authors

GIOVANNI BATTISTA AGUS
Vascular Surgery, Department of Clinical Sciences and Community Health, University of Milan, Italy

CLAUDIO ALLEGRA
Master of Vascular Diseases, S. Giovanni Addolorata Hospital, Rome, Italy

SIMONE ALTOBELLI
Department of Diagnostic Imaging, Molecular Imaging, Interventional Radiology and Radiotherapy, University of Rome "Tor Vergata", Italy

LEONARDO ALUIGI
Center and School of Echography, Maggiore Hospital, Bologna, Italy

GIUSEPPE MARIA ANDREOZZI
Angiology Care Unit of University Hospital of Padua, Italy

PIER LUIGI ANTIGNANI
Vascular Centre, Nuova Villa Claudia, Rome, Italy

ALESSANDRO APOLLONIO
Angiology - AUSL Viterbo, Italy

ENRICO AROSIO
Vascular Rehabilitation Unit, Department of Medicine, University of Verona, Italy

GUIDO ARPAIA
Out-Patients Unit of Angiology, Desio and Vimercate General Hospital, Vimercate (MB), Italy

CLIVE BEGGS
Medical Biophysics Laboratory, University of Bradford, UK

FABRIZIO BENEDETTI-VALENTINI
Department of Vascular Surgery, Sapienza University of Rome, Italy

GIUSEPPE BIANCHINI
Isituto Dermopatico dell'Immacolata, Center of Vascular Anomalies, Rome, Italy

SALVINO BILANCINI
Vascular Diseases Studies Center JF Merlen, Frosinone, Italy

MARISA BONIFACIO
Vascular Medicine, S. Giovanni Hospital, Rome, Italy

DANIEL BRANDÃO
Faculty of Medicine, University of Porto, Hospital CUF, Porto, Portugal

MATTEO BUCALOSSI
Department of Vascular Surgery, Valdisieve Clinic, Pontassieve (Florence), Italy

ALBERTO CAGGIATI
Vascular Medicine Study Center, Rome, Italy

DANIELE CAMILLI
Vascular Surgery, Policlinico Di Liegro, Rome, Italy

SANTE CAMILLI
Vascular Surgery, Private Surgery, Rome, Italy

GIUSEPPE CAMPORESE
Unit of Angiology, University Hospital of Padova, Italy

ENRICO CAPOTORTI
Angiology Unit, Hematology Oncology Department - AUSL, Viterbo, Italy

JOSEPH ANTONY CAPRINI
NorthShore University HealthSystem, Evanston, IL, USA
Department of Surgery, University of Chicago Pritzker School of Medicine, Chicago, IL, USA

MARCO CARDONE
San Giovanni Battista Hospital – ACISMOM, Rome, Italy

ANITA CARLIZZA
Unit of Angiology - S.Giovanni-Addolorata Hospital, Rome, Italy

FABRIZIO CHEGAI
Department of Diagnostic Imaging, Molecular Imaging, Interventional Radiology and Radiotherapy, University of Rome "Tor Vergata", Italy

ANTONIO CHIARAVALLOTI
Department of Diagnostic Imaging, Molecular Imaging, Interventional Radiology and Radiotherapy, University of Rome "Tor Vergata", Italy

ALESSANDRO CINA
Department of Radiological Sciences, "Agostino Gemelli" Hospital, Catholic University of Sacred Heart, Rome, Italy

GREGORIO CINA
Master in Phlebology "Agostino Gemelli" Hospital, Catholic University of Sacred Heart, Rome, Italy

DANIELE CITRARO
Department of Diagnostic Imaging, Molecular Imaging, Interventional Radiology and Radiotherapy, University of Rome "Tor Vergata", Italy

ANDRÉ CORNU-THENARD
Saint-Antoine Hospital, Paris, France

GIOVANNI DAVÌ
Internal Medicine, Universty of Chieti, Italy

COSTANTINO DEL GIUDICE
Department of Diagnostic Imaging, Molecular Imaging, Interventional Radiology and Radiotherapy, University of Rome "Tor Vergata", Italy

MICHELANGELO MARIA DI SALVO
Angiology Unit, "Vittorio Emanuele" University Clinic, Ferrarotto Hospital, Catania, Italy

SILVIA D'ONOFRIO
Department of Diagnostic Imaging, Molecular Imaging, Interventional Radiology and Radiotherapy, University of Rome "Tor Vergata", Italy

SEBASTIANO FABIANO
Department of Diagnostic Imaging, Molecular Imaging, Interventional Radiology and Radiotherapy, University of Rome "Tor Vergata", Italy

ALESSANDRO FAILLA
San Giovanni Battista Hospital – ACISMOM, Rome, Italy

GIACOMO FAILLA
Angiology Unit, "Vittorio Emanuele" University Clinic, Ferrarotto Hospital, Catania, Italy

PIERGIORGIO FALAPPA
Interventional Radiology-Department of Surgery, Bambino Gesù Children's Hospital IRCCS, Rome, Italy

JAWED FAREED
Department of Pathology and Pharmacology, Thrombosis and Haemostasis Research Laboratory, Loyola University Medical Centre, Maywood, IL, USA

ALESSANDRO FIORENTINO
San Giovanni Battista Hospital – ACISMOM, Rome, Italy

ROBERTO FLORE
Angiology Department, Catholic University of the Sacred Heart, Rome, Italy

MASSIMO GALLUCCI
Unit of Angiology, San Giovanni Addolorata Hospital, Rome, Italy

CLAUDE GILLOT
URDIA Anatomy Research Unit, University Paris Descartes, Paris, France

LAURA GRECO
Department of Diagnostic Imaging, Molecular Imaging, Interventional Radiology and Radiotherapy, University of Rome "Tor Vergata", Italy

GIORGIO GUARNERA
Unit of Vascular Surgery, Istituto Dermopatico dell'Immacolata (IDI – IRCCS), Rome, Italy

LUIGI IRACE
Department of Vascular Surgery, Sapienza University of Rome, Italy

EVI KALODIKI
Vascular Surgery Department Ealing Hospital and Imperial College, London SW7 2AZ, UK - Thrombosis and Haemostasis Research Laboratory, Loyola University Medical Centre, Maywood, IL, USA

JAMES LAREDO
Vein Center, George Washington University Hospital, Washington DC, USA

BYUNG BOONG LEE
Department of Surgery, George Washington University, Washington DC, USA

GIANFRANCO LESSIANI
Internal Medicine, Universty of Chieti, Italy

MASSIMO LUCCHI
Vascular Diseases Studies Center JF Merlen, Frosinone, Italy

STEFANO MANCINI
Department of Medical, Surgical Sciences and Neurosciences, University of Siena, Siena (Italy)

ARMANDO MANSILHA
Faculty of Medicine, University of Porto, Hospital CUF, Porto, Portugal

FABRIZIO MARIANI
Department of Vascular Surgery, Valdisieve Clinic, Pontassieve (Florence), Italy

OMBRETTA MARTINELLI
Department of Vascular Surgery, Sapienza University of Rome, Italy

RAUL MATTASSI
Clinical Institute Humanitas "Mater Domini", Centre for Vascular Malformations, Castellanza (VA), Italy

ERICA MENEGATTI
Vascular Diseases Centre, University of Ferrara, Italy

SANDRO MICHELINI
San Giovanni Battista Hospital - ACISMOM, Rome, Italy

LODOVICO MICHELOTTI
San Giovanni Battista Hospital - ACISMOM, Rome, Italy

PIERLUIGI EDGARD MOLLO
Unit of Angiology P.O. Anagni ASL Frosinone, Italy

GIOVANNI MONETA
San Giovanni Battista Hospital – ACISMOM, Rome, Italy

FEDERICA NATONI
Molecular Biology Unit, Hematology Oncology Department - AUSL, Viterbo, Italy

DOMINIQUE NIKI
Department of Diagnostic Imaging, Molecular Imaging, Interventional Radiology and Radiotherapy, University of Rome "Tor Vergata", Italy

FRANCESCO PAOLO PALUMBO
Vascular Surgery, Vulnologic Center, Palermo, Italy

RITA PEPE
Unit of Angiology, S. Eugenio Hospital, ASL RmC, Rome, Italy

GLORIA PESSINA
Molecular Biology Unit, Hematology Oncology Department - AUSL, Viterbo, Italy

FEDERICA POMELLA
Branca Angiologia, Poliambulatorio Specialistico SUMAI ASL Frosinone, Italy

MANLIO PRIOR
Vascular Rehabilitation Unit, Department of Medicine, University of Verona, Italy

DIDIER RASTEL
Selurl Philangio, Grenoble, France

GIOVANNI SIMONETTI
Department of Diagnostic Imaging, Molecular Imaging, Interventional Radiology and Radiotherapy, University of Rome "Tor Vergata", Italy

MATTEO STEFANINI
Department of Diagnostic Imaging, Molecular Imaging, Interventional Radiology and Radiotherapy, University of Rome "Tor Vergata", Italy

FRANCESCO STILLO
Center of Vascular Anomalies, Guarnieri Clinic, Rome, Italy

MAURO TAMBURINI
Center and School of Echography, Maggiore Hospital, Bologna, Italy

LORENZO TESSARI
Foundation Glauco Bassi, Trieste, Italy

MIRKO TESSARI
Vascular Diseases Centre, University of Ferrara, Italy

PAOLO TONDI
Angiology Department, Catholic University of the Sacred Heart, Rome, Italy

JEAN-FRANÇOIS UHL
URDIA Anatomy Research Unit, University Paris Descartes, Paris, France

MASSIMO VAGHI
Hospital "G. Salvini", Centre for Vascular Malformations, Garbagnate Milanese, Milan, Italy

PAOLO ZAMBONI
Vascular Diseases Centre, University of Ferrara, Italy

Contents

PART I

GENERAL CONCEPTS

1 CLINICAL EMBRYOLOGY OF THE VENOUS BED OF THE LOWER LIMBS

A. CAGGIATI

GENERAL

The development of the venous bed of the lower limbs is divided into three stages.

Early embryonic phase. – The first phase is characterized by the presence of a network of undifferentiated vessels that simultaneously supply blood to and drain blood from the precursors of the limb.[1]

Late embryonic phase. – Subsequently, the microvessels functionally differ from each other in arteries and veins, while still retaining morphologically similar walls.[1] The course of the veins is slow to stabilize and undergoes continuous phenomena of regression and fusion, as well as the gemmation of new collectors. At the end of the first trimester of pregnancy, the venous vessels appear different in structure and stabilized in the course. This will be maintained during both the intra- and extrauterine life.

Fetal phase. – In the second and third trimester of intrauterine life, the definitive veins undergo remodeling phenomena regarding their size, structure of the wall and valvulization. These remodeling phenomena will continue even after birth (Figure 1.1).

EARLY EMBRYONIC PHASE, ALIAS RETICULAR PHASE

In the early embryonic stage, a network of undifferentiated vessels supply and at the same time drain the precursor of the limb (Figure 1.2).[2] If a developmental arrest occurs at this stage, real ve-

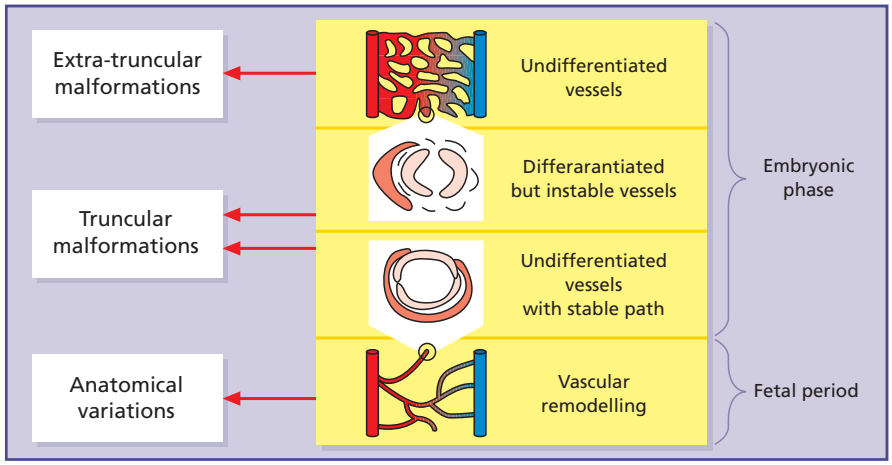

Figure 1.1 – Development of the venous bed.

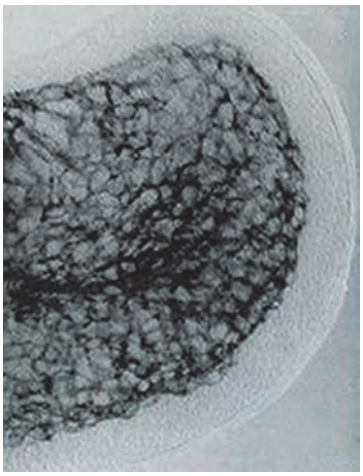

Figure 1.2 – The network of undifferentiated vessels that supply and drain the precursor of the limb.

nous trunks will not be formed as the vascular bed maintains the primitive undifferentiated reticular form. These vessels retain all of the evolutionary potential of mesenchymal cells and these malformations may therefore appear or worsen at any age, even after birth (due to hormonal phenomena or local trauma). Since in these cases the main venous trunks are free of significant alterations, these developmental defects are called *extratruncular venous malformations* which must therefore be considered real embryonic tissue remnants of mesodermal origin that retain the characteristics of the mesenchymal cells (angioblasts).[1] This explains why these lesions carry a significant risk of recurrence, especially after partial excision or incomplete treatment. Besides hemodynamic impact, extratruncular lesions may be present as infiltrating lesions possibly causing mechanical compression to surrounding tissues and organs.

LATE EMBRYONIC STAGE, ALIAS TRUNCULAR PHASE

The first vessels that differentiate into veins develop along the margins of the limb bud and take their name of marginal veins, one medial and one lateral (Figure 1.3).[3] A vascular central axis which accompanies the so-called "axial nerve", (the sciatic nerve for the lower limb) develops later. The artery and vein called "sciatic" course at the center of the limb bud and gradually assume the predominant hemodynamic role. Subsequently the "*pre-axial*" nerve (ventrally to the sciatic) and the "*post-axial*" nerve (dorsally to the sciatic) also develop in the precursor of the limb, both accompanied by a dense venous plexus (Figure 1.4). In particular, the pre-axial nerve is the femoral nerve and the femoral vein and the great saphenous vein will develop from the venous plexus that accompanies it. The post-axial nerve corresponds instead to the lesser *ischiatic nerve* (alias, the cutaneous posterior femoral nerve) and the small saphenous vein and its thigh extension [4] will develop from the venous plexus that accompanies it. These three systems are connected by anastomoses from which important structures such as the deep femoral vein and popliteal artery develop. Once the pre-axial and post-axial systems develop, the hemody-

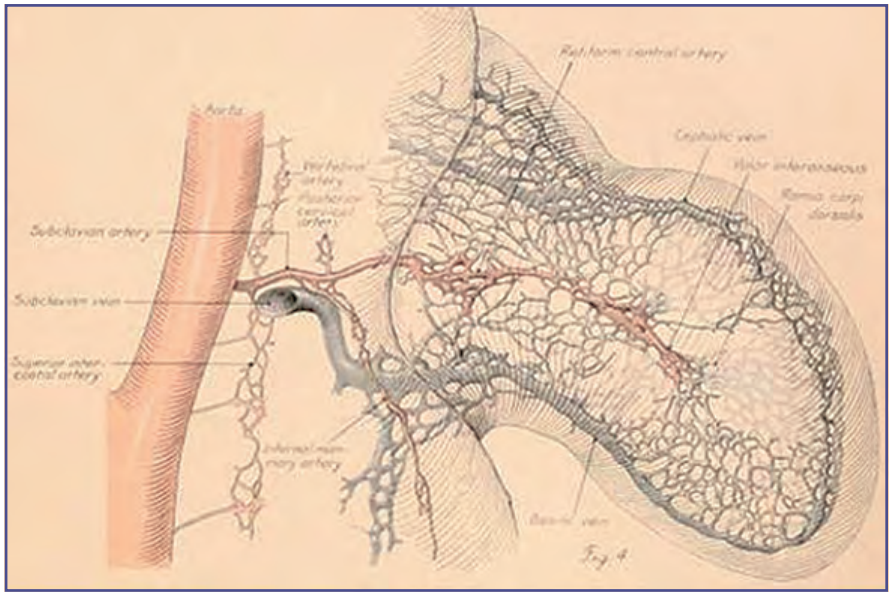

Figure 1.3 – Drawing representing the vasculature of the pig embryo upper limb at a stage corresponding to the fifth week of intrauterine life in humans (modified from: Woollard, 1922).

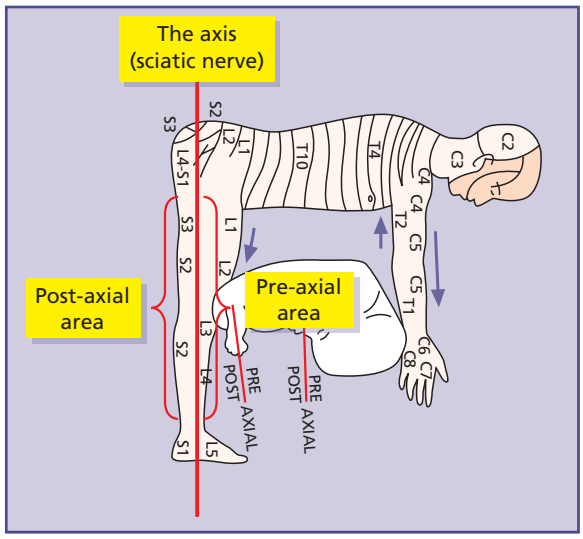

Figure 1.4 – Drawing representing the topography of the embryonic veins according to the path of the axial nerve (sciatic).

namic role of the axial system decreases and the axial vein itself regresses to the simple function of *vena nervorum*.

Note. The exact evolutionary sequence of the venous system is not well known. It should, in fact, be noted that most of the studies on venous embryology of the limbs were not performed on humans but on other mammals or other species. In some cases the upper limb has been studied. In addition, most of our knowledge comes from studies conducted more than a century ago, based on sporadic observations that were not repeated or verified over time.

The "truncular form" of venous malformations occurs when development stops during the "late stage" of the embryonic development. It consists of a persistent fetal remnant vessel (e.g. the sciatic or the lateral marginal veins) or as a defective vessel trunk (e.g. venous aneurysm, webs or stenosis of large veins). Truncular lesions do not grow or proliferate because the abnormal vessel lost the embryonic characteristics of the mesenchimal cells. In turn, truncular lesion may imply more serious hemodynamic consequences than extratruncular ones.

Fetal stage

During the second and third trimester of intrauterine life the course of the veins is stable.

Changes occurring in this period affect vein morfology and functionality. These changes depend on hemodynamic, physiologic or pathologic phenomena, and may therefore continue even after birth. Already fifty years ago, the Swiss Anatomist Rickenbacher stated: "*The definitive venous patterns develop to facilitate those segments of the venous net which represent favourable hemodynamic shunts. In turn, unfavourable shunts are demolished*". Therefore, these phenomena, therefore, determine the true final appearance of the venous bed, as it will be present in the adult. Changes occurring during this long period have not been considered by eminent venous embryologists.

The main changes that occur during the fetal period relate to the caliber, connections and valvulations of the definitive veins.

Variations in caliber are frequent in normal veins, especially in superficial ones.[5, 6] As an example, the caliber of a normal saphenous vein ranges between 2 mm and 6 mm. Segmental hypoplasia and aplasia of the saphenous trunks are more frequent in varicose limbs. This led to the assumption that saphenous aplasia may be a predisposition to the onset of varicose veins.[6]

The great anatomical variability between individuals concerns the pattern of connections of the main veins, the most striking example being the saphenous endings (Figure 1.5) where the connections of tributaries with main trunks are crucial for the pathophysiology and treatment of varicose disease.[7, 8]

Finally, the greatest inter-individual differences concern the different number of valves found in normal veins.[9, 10] Venous valves (VV) appear at 3-4 months of intrauterine life, especially in the vessels adjacent to the heart and muscles. The VV increase in number during the prenatal life. Differences with regards to distribution and characteristics of VV in different areas of the human body start during the intrauterine life and continue after birth. In 1981, Maros pointed out that "[…] *certain findings suggest a reorganization of the venous valves which are frequently met in fetus. The close relation between hemodynamic mechanisms and the blood guiding structures may explain the changes (disappearance or persistence) of venous valves in some areas* […]". According to Kampmeier and Birch, the earliest valves of the lower extremity appear in the deep veins of the femoral trigone and popliteal fossa and in the upper end of the great saphenous vein.[11]

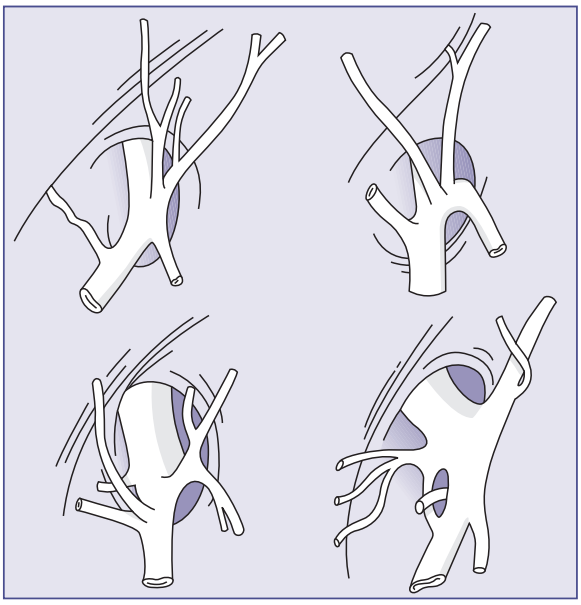

Figure 1.5 – Variability of tributary veins number and connections at the ending of the great saphenous vein.

Despite the rare cases of the avalvulia syndrome (characterized by the absence of valves in both deep and superficial veins),[12] it is quite common to observe great inter-individual differences in the number of venous valves in normal limbs. For example, the number of valves along the great saphenous vein varies between 7.3±2.3 and 2.4±0.83. Considering the relevant hemodynamic role of valves in preventing venous insufficiency, it has been postulated that a lesser number of valves may provoke varicose veins. Similarly, relevant difference in valvulation have been reported in the area of the terminal saphena, common femoral and external iliac veins.[7] For example, in 30% of limbs, no valves are located in the femoral or external iliac veins above the saphenous opening. Again, in about 30% of limbs, the pre-terminal valve of the saphenous vein is missing. Both conditions are relevant from the hemodynamic and surgical points of view.[13]

CONCLUSION

Changes occurring during the fetal period were poorly considered by eminent embryologists. However, they are responsible for those differences marked as interindividual, regarding the size, number, termination, connections and valvulation of the main veins occurring even in normal limbs. These changes are of crucial importance in pathologic conditions like varicose veins.

REFERENCES

1 Lee BB, Bergan J, Gloviczki P, *et al.* Diagnosis and treatment of venous malformations. Consensus document of the International Union of Phlebology (IUP)-2009.International Union of Phlebology (IUP). Int Angiol 2009;28:434-51.

2 Lewis FT. The development of the veins in the limbs of rabbit embryo. Am J Anat 1905;5:1-120.

3. McClure CFW, Butler EG. The development of the vena cava inferior in man. Am J Anat 1925:35:331-83.

4. Barberini F, Cavallini A, Caggiati A. The thigh extension of the small saphenous vein: a hypothesis about its significance, based on morphological, embryological and anatomo-comparative reports. Ital J Anat Embryol 2006;111:187-98.

5. Ricci S, Caggiati A. Does a double long saphenous vein exists? Phlebology 1999;14:59-64.

6. Caggiati A, Mendoza E. Segmental hypoplasia of the great saphenous vein and varicose disease. Eur J Vasc Endovasc Surg 2004;28:257-61.

7. Caggiati A, Bergan JJ, Gloviczki P, *et al.* Nomenclature of the veins of the lower limbs: Extensions, refinements and clinical application. J Vasc Surg 2005;41:719-24.

8. Caggiati A, Bergan JJ, Gloviczki P, *et al.* Nomenclature of the veins of the lower limbs: an international interdisciplinary consensus statement. J Vasc Surg 2002;36:416-22.

9. Basmaijan JV. The distribution of valves in the femoral, external iliac and common iliac veins and their relationship to varicose veins. Surg Gynecol Obstet 1952;95:537-42.

10. Caggiati A, Phillips M, Lametschwandtner A, *et al.* Valves in small veins and venules. Eur J Vasc Endovasc Surg 2006;32:447-52.

11. Kampmeier OF, Birch LF. The origin and development of the venous valves, with particular reference to the saphenous district. Amer J Anat 1927;38:451-99.

12. Lindvall N, Lodin A. Congenital absence of valves in the deep veins of the leg. Acta Dermato-Venereologica Scand 1961;41:45.

13. Caggiati A, Rosi C, Heyn R, *et al.* Age-related variations of varicose veins anatomy. J Vasc Surg 2006; 44:1291-5.