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Contents

Editor’s Introduction  II
Richard Schol

Journal of EMSA ...
Message from the President  1
Daniel Keszthelyi
Medical Education  3
Salmaan Sana
Medical Science  4
Richard Schol
Medical Ethics  5
Şahin Khanıyev
Are We Made of Steel?  6
Samuel dos Santos Ribeiro

... And Scientific Affairs
Monoclonal Antibodies in Angiogenesis Inhibition—Bevacizumab and Vatxin to Fight Cancer  21
Aleksandar Kibel
Circulating Acetylcholine Revisited: Physiological and Clinical Relevance  26
José Pedro G. L. Almeida
The Use of Panax Ginseng in Sports  33
Mark Ellis; Anthony Serracino-Inglott, Professor and Kirill Micallef-Stofrue, MD
Gujjar Lung—A Disease Mimicking Miliary Tuberculosis  40
G. Hassan, Waseem Qureshi, Kadri SM, G. Q. Khan, Sona-ul-lah, Rashid A. Rather, and Mir Suhail Omer

... On Medical ...
Medical Peace Education in Europe  8
Eva-Maria Schwienhorst, Cäcilia Buhmann, Klaus Melf, and Stephan Kolb
Medical Students’ Ethical Knowledge, Awareness and Medical Ethics Education  11
Nur Hursoy, Oguzhan Altiparmak, Berkan Kaplan, Ayfer Aslan, Nida Erol, Elvan Ciftci, Gamze Gezgen, and Şahin Khanıyev
Internet  18
Richard Schol
Scientific Biomedical Student Congresses in Europe  19
Floris Imann
Dear readers,

Science and education are the two main pillars on which the medical profession is built. JEMSA’s main goal is to support students who write about their scientific research projects throughout the process of publication. Next to this we try to produce publications on both before mentioned pillars, to show medical students in Europe which topics their colleagues are working on and to kindle their enthusiasm so they will do medical research in the field of education or science.

Ethics is the third working field of EMSA, so we strive to inform our readers on this subject as well. The outcome is an article about the knowledge and preferred education of ethics in Turkey. Furthermore some basic science articles and reviews are published in this issue, next to an education minded article. As we will work with fellow healthcare professionals in the future, EMSA is working together with other student organisations, such as the European Pharmaceutical Students’ Association (EPSA), which resulted in an exchange of scientific manuscripts. In EMSA, we are not only looking at our own continent, we are also concerned with medical issues outside of Europe. Therefore we are very much willing to cooperate with scientist from other parts of the world.

In comparison with JEMSA’s Spring Edition 2006, this issue contains more information about the projects EMSA is working on and the main policy papers EMSA has written last year. We would like to inform everybody in Europe, who is interested in medical student issues, about the topics EMSA is working on and offer them the opportunity to give us some feedback, to join us and to collaborate with us.

JEMSA’s 2007 Edition is the first issue which comes from my hands. This wouldn’t have happened without much support and guidance from the people around me. I want to thank those people for all the help I received. Furthermore I would like to thank the authors for their patience and co-operation. I hope all this patience was worth it for you personally. At last my thanks go to the current EMSA European Board and Thieme Publishers – without these two, JEMSA’s 2007 Edition would have never been born.

Best Regards,

Richard Schol
JEMSA Chief Editor 2007
Message from the President

European Medical Students' Association (EMSA): By Medical Students for Medical Students

Daniel Keszthelyi
President 2006/07 EMSA European Board, European Medical Students' Association

"Europe's wealth lies in the knowledge and ability of its people; that is the key to growth […] For we know, Europe is our common future."
(Quote from the Declaration on occasion of the fiftieth anniversary of the signature of the Treaties of Rome, 25th March 2007, Berlin)

The European Medical Students' Association (EMSA), founded in 1991 and registered under Belgian law, seeks to improve the health and quality of care of the citizens of Europe, by acting as a conduit for increased interaction and sharing of knowledge between European medical students in the fields of medical education, ethics and science. EMSA currently has 63 active Faculty Member Organisations representing the interests of medical students in 22 countries across the European Union and geographical Europe, enjoys the support of the European Commission and is also proud to have working collaborations with many European institutions.

The European counties are experiencing times of major educational and health reforms, affecting nearly all members of society, including medical students. Those stakeholders, who are able to unite their voices, will be able to maintain a better position in the new status quo. Therefore, there has never been a greater need for the student voice to be heard in unity. This underlines the importance of increased interaction between medical students across geographical Europe through EMSA. Over the past years, EMSA, by the hard and devoted work of its members and enthusiasts, was able to obtain a high reputation in the European arena, by establishing contact with organisations on the European level influencing policy making, as well as a great number of European international non-governmental youth organisations. We expect these contacts of EMSA to gradually increase both in number and intensity over the upcoming years.

EMSA is an Associated Organisation of the Standing Committee of European Doctors (CPME), the representative body of over 2 million physicians in Europe. As such, EMSA strives to represent the voice of the European medical students also on behalf of the International Federation of Medical Students' Associations (IFMSA). Practically, this means that EMSA can introduce documents dealing with important issues related to medical students to the CPME, which can decide to endorse them, meaning the European doctors adopt it as a policy of their own and lobby for it accordingly at the Institutions of the European Union, in specific, the European Parliament. This means, when the Members of the European Parliament try to create European legislation when it comes to for instance implementing changes regarding the European Higher Education Area, they will not forget about the medical students’ voice.

This is the case with our document the 'Albufeira Resolution on Medical Students' Rights in Europe' from the EMS Council meeting in January 2006, in Albufeira, Portugal and the joint IFMSA-EMSA document 'European Core Curriculum—the Students’ Perspective' from the Bologna Process Follow-up Workshop in July 2006, Bristol, which were both endorsed unanimously (1) by the Board of the CPME on the 17th of March 2007 at its meeting in Warsaw (see http://www.cpme.be/policy.php).

We hope these documents will hence serve as a basis in ultimately all European countries when re-evaluating and reforming medical education.

This just highlights that the high quality of work executed by the medical students of Europe and EMSA is highly appreciated and warmly welcomed by representatives of our future profession. Congratulations!

Our work in this field will continue, as the next joint IFMSA-EMSA Bologna Process Follow-up Workshop in Amsterdam will address the Bachelor-Master degrees in medical education (see www.bolognaamsterdam2007.com).

The other way to influence decision making is to lobby for our own position when it comes to elaborating policies affecting all doctors. This was the case with our policy paper created together with the Permanent Working Group of Junior Doctors (PWG) regarding the European Working Time Directive (EWTD). The CPME applauded our PWG-EMSA paper and would like to use it as reference work in the future. Nevertheless, the delegates of the three organisations sat down to construct the CPME-EMSA-PWG joint position paper, which was also adopted by the CPME Board and will be taken forward as such when it comes to lobbying for this issue which will influence our future professional lives.
Medical students’ input is expected to exponentially increase also within the Thematic Network on Medical Education in Europe (MEDINE). In the MEDINE 2 application, currently being developed, EMSA seeks, by inviting a number of organisations to reach not only a broad spectrum, but also a very high-quality level of representation (see http://www.bristol.ac.uk/medine/).

Advocating for the medical students’ opinion does not stop with the collaboration with our professional partners on the European level, as important decisions are also made nationally and locally on the faculty level. EMSA also tries to reach the most appropriate student bodies in terms of their position in policy making on a national level by inviting the National Member Student Organisations to the European Medical Students’ Council, a politically neutral body created by EMSA, which acts as a facilitator in developing common goals and strategies to be implemented on the European level. The most meeting, held in Heidelberg, did address the issue of ‘Information to Patients’ (see www.emscouncil4.org).

EMSA is not only a tool, by which one has the chance to express ideas, but also a provider. It provides you a chance to publish a scientific article in the Journal of EMSA on Medical and Scientific Affairs and to intensify your research knowledge. EMSA gives you the possibility to develop a European identity and increase inter-cultural communication by programmes such as the Twinning Project and Eurotalk, to develop your skills in the field of medical ethics to become a better doctor. EMSA also contributes to society: it is an advocate of health education and aims to facilitate the development of a health-conscious society and thus to improve the overall health status—these projects include the Teddy Bear Hospital (a joint EMSA-IFMSA initiative) as well as an integrate programme Teaching the Next Generation, aiming for prevention of obesity and tobacco abuse among others in collaboration with the European Pharmaceutical Students' Association (EPSA).

So esteemed EMSA members, medical students of Europe, it goes without saying how important it is for us not only to be aware and be involved in the current European developments, but also to find the best way to try to influence them according to our position by having one, strong, united voice.

I am proud to say we have succeeded in that, so I congratulate everyone who has contributed to this work with passion and devotion and I strongly encourage all of you to continue your involvement and to keep up high quality of work! This will lead us to our ultimate goal: “One Europe, one voice.”

Europeally yours,

Daniel Keszthelyi
President 2006/07
EMSA European Board
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Medical Education

What’s new in EMSA on the Medical Education Front?

Salmaan Sana
EMSA Medical Education Director
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The Bologna Process Conference 2007 meeting

From the 5th to the 9th of July, EMSA together with our partner the International Federation of Medical Students Association (IFMSA) will be hosting the Bologna Process conference in Amsterdam. The topic will be a much discussed and controversial Bachelor and Master program. Of course, as being active students and ones that not only like to have a critical view on everything, we intend to have very constructive outcomes and be able to have some influence on the policy makers with our perspectives. More information on www.bolognaamsterdam2007.com.

MEDINE: Medical EDucation IN Europe (www.bristol.ac.uk/medine)

MEDINE is the Thematic Network on Medical Education in Europe. It addresses educational, institutional and quality issues in European medical education. It works within the framework of European initiatives—the Bologna Declaration, European Credit Transfer System (ECTS), Diploma Supplement, the Tuning project—and previous work in medicine by the European Commission, AMEE, AMSE, and WFME.

The former medical education director together with the current EMO-LO are both very active within Taskforces of MEDINE. EMSA is working on a plan on providing continuity of student input within these task forces. This is still in development, although news about this will be coming soon. More information on www.bristol.ac.uk/medine.

“Education Unlimited” (EDUNL). A project from AEGEE

The project Education Unlimited! is aiming at greater involvement of young people in designing their learning experience. With this project we will express and implement ideas on what and how we want to learn through our education. Education Unlimited! focuses on the impact of reforms within the Bologna Process on students active in youth NGOs, need for recognition of experience gained through non-formal education, and crucial role of mobility in both formal and non-formal context. EMSA together with many other NGO’s will be playing a role in the expression of these idea’s and the bringing together of Formal and Non Formal Education.

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Medical Science

Richard Schol
EMSMA Medical Science Director
Academic Medical Center, University of Amsterdam, The Netherlands

The Medical Science pillar of EMSMA carries out a lot of activities. As research is important for our future as medical professionals, EMSMA focuses on the promotion of medical science among students, increasing the quality and amount of research done by medical students and spread important news from the world of science in the students community.

Therefore EMSA has several activities, like this journal (JEMSA), research projects with EPSA (European Pharmaceutical Students’ Association) and lobbying within the European Commission. Last year EMSA developed a couple of new projects, for example the Network of European Student Conferences (NEMSC) and an internship program (SciF).

NEMSC

This is a network founded by ESC Berlin, ISCOMS Groningen and EMSA in April 2007. With this network we focus on more mobility of medical students across Europe by establishing exchanges between the two research centres behind these conferences. Furthermore, we will improve the quality of student conferences within Europe by training the Boards of the conferences and organisations in this network and by working on quality improvement of the abstracts submitted to the scientific boards of the conferences. This network will establish a website which will be a scientific student e-platform were students can find information on how to publish, were to publish, links to science based websites and create their own scientific profile. It is our intention to increase the popularity of research among European medical students by joint promotion and show the beauty of participating in (bio)medical research projects.

The three parties in this network are looking forward to welcome more conferences in the future by stimulating and assisting them to increase their stability, improve the quality of submitted abstracts and grow in participants.

SciF

A student learns the most by just practicing. The scientific world is an international one, in which Europe plays an essential role. For students it is important to be aware of the international character of their future careers and which enormous place research has in that career.

Therefore EMSA intends to set up an internship network within Europe for their student members. In these scientific based internships the participant will look further than the walls of their own faculty. In Europe the borders of our countries gets vaguer day by day. And when it is about science, international collaboration and experience is essential. With such an internship program we would like to offer all medical students in Europe such a chance to improve their research and communication skills.

We will start with a couple of internships in the first year but are planning to expand in the future and cover more research fields year by year. In these internships students will participate in PhD projects for a couple of months, in which a student will learn research techniques and dedicate a lot of time towards medical science. By this they will experience the international dimension of science and being able to learn from other cultures.

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Medical Ethics

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Although almost every medical student is aware of the importance of ethics, it is still not getting the attention it should. This is why "Medical Ethics" is one of three pillars of the European Medical Students' Association. We as tomorrow's physicians should gain ethical knowledge, skills and attitudes in this modern day, so that we can improve our patient's health in the best way. Here you can find some news about the most important activities in the field of medical ethics by EMSA.

Medical Ethics Projects

Having kept in contact with the former Medical Ethics Director, previously initiated EMSA Medical Ethics Projects, such as "Visitor Service for Nursing Home Residents", "Reporting System for Critical Incidents and Suspected Medical Errors", are attempted to be reanimated and continued. For that, a Medical Ethics Projects' Progress Report is prepared to assess our development and to draw new roadmap. It is also planned to prepare an EMSA Medical Ethics Activities Handbook which will include both previous projects and new project proposals that can be discussed and developed further. Relevant information about all those projects can be found on the website (www.emsa-europe.org).

Topic of the Month

Everyone likes discussions. It is also known that ethical issues can be better understood and evaluated via discussions. "Topic of the Month" is such an activity that medical students get a chance to share their opinions and experiences on monthly selected ethical topics via web-based forums. Topics are chosen from challenging issues of medical ethics in relation to hot topics of today, such as autonomy, end of life, sex determination, relationship with industry etc.

Medical Ethics in Medical Education

We all agree upon that ethics education is very important for our future career. This is also a new initiative created to define our concerns, interests and to put forth suggestions for better ethics education. The motive of this initiative has been created so that we as medical students can define our needs more realistically and propose new tools for ethics education which can satisfy and encourage our colleagues more effectively rather than the current status. A milestone of this initiative is the document created by the participants of "European Youth & Womens Health" Training Course in Ankara, in March, which includes a number of practical recommendations regarding ethics education and can be used to take a step forward by European medical students. Therefore, we can come up with a well-structured proposal to implement change in our curricula as European medical students.

Collegial Consultation

This is also available for medical students who have questions regarding medical ethics. The Medical Ethics Director functions as a bridge to direct your questions to the experts and also transmits their opinions and answers to you.

Visit Medical Ethics pages on EMSA website, and join us in proceeding on the road of becoming tomorrow's "more aware" doctors!

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Are We Made of Steel?

Samuel dos Santos Ribeiro  
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Mankind has found a funny way to interact with each other. Since the dawn of history, societies have used work as the best currency to obtain goods or money. Work has become a central aspect of life and has generated a curious paradox, where the more you work, the less time you have to enjoy the extra money you have obtained from it. Since the first Convention of the International Labour Organisation in 1919, society has thrived to reach a balance between work and personal lives. Governments have a broader view of the issue and prefer to say that we are (or will be) part of a regulated workforce. As the EU grows, the inequalities between nations must be tuned on a European Level. Having this in mind, the Commission has recently released a Green Paper on the Future and the Modernising of Labour Law.

Regardless of national and personal interests, the question must be asked: to what extent can we work without harming ourselves and the ones around us? To answer this question (and the before mentioned green paper) from a future doctor's perspective, EMSA and the Permanent Working Group of Junior Doctors (PWG) decided to review what research has been done on this topic, results which I will summarize in the following lines.

The Working Time Directive has divided Doctors since very early in European history. Junior doctors in the EU are still put aside from the European Working Time Directive (EWTD) and such exclusion leaves the decision of the amount of time they work daily completely up to national governments. We have reached a situation where the hospital workforce is essentially junior doctor driven, especially during night shifts.

Nevertheless, this is not only a forced condition. Doctors do sometimes opt to work extra hours on a voluntary basis to obtain a better income. This case is extreme in the USA, where maximum limits of 80 or even 100 hours have been contested as insufficient. If, on one hand, we clearly state that our patients should maintain a balance between work and rest, doctors sometimes believe that their advice does not apply to themselves.

A new concept of "latent" errors [1] illustrates that the deficiencies in training and management affect the working environment and, consequently, people become more susceptible to making mistakes. At present there is a growing amount of published research in this field, particularly in relation to work hours of resident doctors in training. There is now direct evidence that excessive hours of work in residents are associated with disrupted sleep patterns, increased incidence of failures due to lack of concentration [2], increased incidence of motor vehicle accidents [3] and increased numbers of serious medical errors [4].

When studying the effects of an on-call work night, even when sleep was not disrupted by the service, it seemed often limited and most of all fragmented [5] and the increase in sleep on the following night is limited to 20 minutes on average. When the day following an on-call is a normal working day, the motor activity is only reduced in the evening, probably owing to the fact that fatigue and sleepiness are hidden, during the day, by work demand. This gives doctors the false effect of being able to cope with a sleepless night, a false "man of steel" effect. Dinges [6] studies even show more curious results, when it calls to the fact that many people are not biologically apt for night work and that even those who cope require up to a 3-day adaptation period to recover from overnight periods of work.

For Minors and Waterhouse [7], a minimum of four-hour sleeping period at night is necessary to maintain the 24-hour synchronization of the body heat. From a subjective point of view, all the parameters (daytime quality, irritability, sleepiness, concentration, fatigue and mood) are altered on the day following the on-call. The poor quality of the overnight on-call, as shown in the wake-sleep diary, coincides with data collected amongst engineers on stand-by that expect to be woken up. On the second day, post on-call, despite a night when sleep is recovered, fatigue is still present and mood as well as concentration is still deteriorated. Those persistent negative effects suggest that the recovery has been incomplete as demonstrated above. The return to normal cognitive functions only occurs after 2 nights of rest recovery. This study stresses the role played by a sufficient post on-call rest in order to insure the patients' safety as well as the physicians' health. The introduction of this rest requires the implementation of a restructuring within hospital units [8].

Sleep, set like clockwork, regularly occurs in two periods, over a 24-hour timeframe, by night and between 13:00 and 15:00 [9]. A disruption of this cycle has, as a consequence, diminished appetencies in the following days. Studies on pilots crossing 6 time zones while flying have revealed that the ability to perform simple tasks is recovered only within 3 days and that more complex tasks require more than 5 days to be recovered [10]. Most accidents in the automotive industry occur during or right after a working night [11]. Even more so, as Dawson and Reid have concluded, the psychomotor performance of an individual after a 24 hour period of wake is the same as that of an individual with a blood-alcohol level of 1 g/l [12]. As stated before, any rest that may be done during on-call time is not effective. After a sleepless night, some individuals feel very tired in the morning but do not however feel like going to bed: this is what is known as the circadian effect and has only to do with the fact that the body has its own vigil-sleep hormonal cycle, that although inhibits slightly the will to go to bed, does not enhance the ability to act, but instead merely mules the body in a false feeling of alertness. The minimum required to maintain alertness and adequate cognitive functions is estimated to be 5 hours [13].

Studies, analogous to the above mentioned, clearly show the need for a strong working time directive and the increase of an
understanding, by the medical workforce, of the negative effects of overwork on performance. This is also a clear risk against patient safety, and patients are unjustifiably powerless regarding this problem, since they are never informed of the amount of rest their doctors—that are treating them—have had!

Of course, this is unfortunately not an easy issue to tackle. More studies have to be done to develop the optimal system to integrate a safe working time directive amongst doctors, without outbalancing the quality of life once more. After all, we are not made of steel!

If you are interested in this topic, you may find more information on our website: www.emsa-europe.org.

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9. EMS document on Working time & medical on calls (F04/22 EN)

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Medical Peace Education in Europe

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Abstract

A new academic discipline is establishing itself in universities and medical schools around the world that promises to profoundly enrich our curriculum and allow medical practitioners to effect positive change in the world. This new discipline is strongly related to public health, medical ethics and social medicine. The following article will convey background knowledge on the development of Medical Peace Education and elaborate on the theoretical foundations. It aims to give an overview of existing courses in Norway, Germany, the Netherlands, and Spain, and a pan European internet-based project, and wishes to inspire universities where such courses are not yet taught. An emphasis is laid on the role of medical students in the development of courses in Medical Peace Education.

The Concept of Medical Peace Education

A new academic discipline is establishing itself in universities and medical schools around the world. It promises to profoundly enrich our curriculum and allow medical practitioners to effect positive change in the world. This new discipline is strongly related to public health, medical ethics and social medicine. As recently several universities and medical schools have instituted courses related to peace and conflict, this article aims to give both an insight into this academic discipline and an overview of existing efforts throughout Europe. It also wishes to inspire universities where such courses are not yet taught.

First of all we have to address the question: What is Medical Peace Education?

It is best explained as education that aims to give health professionals the tools and knowledge to improve health of their patients and societies through the prevention and mitigation of violent conflicts and the promotion of peace. The idea derives from the concepts of ‘Health as a Bridge to Peace’ by WHO (www.who.int/iac/techguidance/hbp/en/index.html) and of ‘Peace through Health’ developed at McMaster University in Canada in the 1990s (www.humanities.mcmaster.ca/peace-health), which both focus on the particular role of health professionals in peace building. In recent years, there has been accelerating interest in this field, also labelled as ‘Medical Peace Work’ or ‘Peace Medicine’, leading to more publications, courses and conferences.

To give a better idea of what is being taught in these courses; let us look at the scope of Medical Peace Education. Topics include such issues as disarmament and weapons control, the prevention and mitigation of direct and indirect health consequences of war, root causes of violent conflict, violence prevention, medical ethics, human rights, globalisation and militarisation, refugee health, or the role of health professionals in peace building and humanitarian assistance, in poverty alleviation and sustainable development.

But why are health professionals involved in different forms of peace work and why should this be part of the medical curriculum? Firstly, violence is a profound public health problem and war in particular is estimated to become the 8th most common cause of mortality and morbidity by the year 2020 [5]. Secondly, in a globalising world every doctor will in one way or another be in touch with patients who have suffered the consequences of violent conflict, either because the doctor is working in a war torn society or because s/he sees patients who have migrated from areas of violent conflict. Thirdly, it is our social and ethical responsibility as physicians to prevent illness and death; therefore we have a professional obligation to bear witness of the inhuman consequences of violent conflicts and to prevent reduce violence as a way of maximizing human health and well-being. Fourthly, the medical profession has distinctive assets for peace work; as health professionals we aspire to certain ideals, such as altruism, empathy, humanism, and impartiality which gives us access to conflict areas. We have useful expert knowledge of epidemiology, public health and psychology, as well as skills in communication of health hazards, which puts us in a unique position to point out injustices, develops strategies to violence prevention and to contribute to sustainable peace building [1]. This is the theoretical foundation for academic efforts in Medical Peace Education, as well as for the activism of NGOs such as the Nobel Peace Prize winning International Physicians for the Prevention of Nuclear War (IPPNW).

As future physicians, we have no choice but to be faced with the health consequences of war and violent conflict in our professional life, and we may have the chance to play a vital role in preventing or easing those devastating consequences due to our unique role. The need to cover these aspects in our medical studies thus becomes more than obvious.

One remarkable fact about courses on issues of peace and conflict is that students have played a major role in the development of Medical Peace Education. Students from IFMSA (International Federation of Medical Students Associations) and from IPPNW were some of the first to request education in global health questions including issues related to violent conflicts,
and they helped implement such courses in Europe (e.g. Germany) and North America.

Overview of Existing Courses in Europe

Our overview of Medical Peace Education here is limited to those courses that focus on the health effects of violent conflict as well as their prevention. This should not detract from the importance of general courses in International Health, Global Health, Public Health, etc. An extensive list of these courses can be found at www.globalhealtheducation.org.

The different formats and patchwork implementation of peace-relevant courses at this point are due to the dependence of a combination of available teaching skills or strong student organisations and a willingness of the particular universities to implement and finance the initiatives.

The precursor for the latest developed courses in Norway and Germany are the Peace through Health courses at McMaster University (www.humanities.mcmaster.ca/peace-health) and University of Waterloo in Canada (www.grebel.uwaterloo.ca/pacs301) that have been established in 2004 and 2005 respectively.

University of Tromsø, Norway

The University of Tromsø began offering a spring elective in ‘Peace, Health and Medical Work’ in 2005. The course objective is to create awareness about the potential role of health professionals in violence prevention and sustainable peace building. Main target groups are medicine, health science and social science students who are interested in health-related international work. The elective is structured along a circle of global medical peace work and focuses on the peace building capacities of health professionals before, during and after violent conflicts (Fig. 1).

Students learn about different threats to peace and human security, such as the proliferation of arms and unequal access to healthcare. They are introduced to peace work-related skills, knowledge and values, and they are trained in various ways in which health professionals can act to counter violence in its different forms and levels. Further, the module covers peace and conflict impact assessment of humanitarian aid and development assistance, and provides theoretical and analytical tools for comprehending basic mechanisms of medical peace work at home or in violence-prone settings abroad. The teaching methods consist of experience-based lectures, case studies, group work, role-playing, a panel debate and a film screening. All the teaching is put together to one intensive training week. In order to gain 10ECTS on Master level the students have to complete the reading of 500 pages of obligatory and 500 pages elective literature, and pass an exam. For more information visit: www.sih.uio.no.

University of Erlangen, Germany

Following the tradition of the courses at McMaster in Canada and Tromsø in Norway, the University of Erlangen established the course ‘War. Trauma. Health—the responsibility of physicians in the prevention of violence and the promotion of peace’ in 2005. It is a 20-hour course imbedded in the medical ethics curriculum as an elective for students in the 4th year of their studies. Delivering a presentation on one of the course topics and submitting a paper is mandatory. Topics include health effects of international sanctions, nuclear weapons, small arms and light weapons, children and war, the role of physicians in torture, and peace building. For more information visit: www.gesch.med.uni-erlangen.de/eth/lehre/wgte/ko.htm.

The course in Erlangen has set an example of how Medical Peace Education can successfully be made part of the curriculum for medical students. At other German universities, students have played an active role in organizing lectures in this field, for example in Ulm, Düsseldorf, Dresden and Berlin.

An attempt to facilitate the implementation of either lectures and seminars or full courses as part of the medical studies in Germany, is the so-called 'IPPNW Academia'. This is a web-based resource of guest lecturers and course topics in order to support students and teachers in the design and organization of teaching units on the above mentioned subjects.

For more information visit: www.ippnw.de.

The European Medical Peace Work Project

With this project eleven European medical peace organizations and teaching institutions wish to strengthen the peace-health field through the development and collection of teaching material. By the end of 2007 they will have produced a 60-hours online course, new educational film material, a textbook and a web-based resource centre for teaching medical peace practice. The website will include databases of existing courses, model curricula, education research, referenced presentations, resource persons, and archives for film, picture and audio material.

Main target groups for the online course are medical students and practicing doctors, and for the resource website academic staff, trainers and other specialists involved in medical education and/or vocational training for physicians. The distance learning package offered to physicians is intended as an online certificate course accredited by European medical associations. For medical students it will be offered as an elective self-study

![Diagram of the circle of global medical peace work.](image)
course which, combined in a blended learning package (including practical skills training sessions), might give 10 ECTS credits. The proposed methodology is problem-based with a participatory action approach, including role-play and case assessment. This pilot project is funded with support from the Leonardo da Vinci program of the European Commission. For more information visit: www.medicalpeacework.org.

Free University and the University of Amsterdam, Netherlands
15 students at the Free University and 30 at the University of Amsterdam are accepted each year for a course in ‘Health and Issues of War and Peace’. This was started in 1992 by the Dutch IPPNW-affiliate NVMD, and include issues such as the health effects and the physician’s role in the prevention of atomic, biological and chemical (ABC) weapons, psychological effects of conflict and war, health and human rights, the role of doctors in conflict situations and peace keeping forces, to name but a few. The course is taught through a series of 20 lectures, and includes a mediation game as well as resolving cases related to health and human rights [3]. For more information visit: www.antenna.nl/nvmp/educas.html.

University for the Basque Region, Spain
Since 2002, a Medicine and Peace course has been taught at the university in Bilbao, in a region affected by a long-lasting violent conflict. Ninety medical students each year take the course, which is comprised of 20 lectures and ten seminars and is aimed for students in their 2nd and 3rd year. Issues include violence and arms trade, weapons systems, human development and human rights, consequences of war etc. In the seminars, students are made familiar with peace and human rights organizations [4].

Conclusion

While this overview of existing courses is necessarily brief and incomplete, it must also be stated that there is much work to be done in the field of medical peace education. Students have been central in implementing these courses, both by clarifying the theoretical link between violent conflict and health, and by expressing to university, faculty and staff that this discipline is important and worth teaching. Students can be very powerful in working towards the development of these courses. It may start with organising a set of extracurricular lectures, and result in working together with faculty members to implement and promote the vital field of Peace Medicine.

Those interested may obtain further insight and meet future collaborators at the international conference ‘Educating Health Workers for Peace’ from 13th to 15th June at the University of Tromsø, Norway [http://uit.no/sih/8989].

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University of Tromsø, Norway: Peace, Health and Medical Work
www.sih.uit.no

University of Erlangen, Germany: War.Trauma.Health
www.gesch.med.uni-erlangen.de/eth/lehre/wgte7ko.htm

‘IPPNW Akademie’ in Germany
www.ippnw.de, also www.ippnw.org

European Medical Peace Work Project
www.medicalpeacework.org

Free University and University of Amsterdam: Health and Issues of War and Peace
www.antenna.nl/nvmp/educas.html

University College, London: Bachelor in International Health
www.ihmec.ucl.ac.uk

Collection of courses in global health for undergraduate medical students
www.globalhealtheducation.org

International Federation of Medical Students’ Associations
www.ifmsa.org

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Medical Students’ Ethical Knowledge, Awareness and Medical Ethics Education

Critique of Medical Ethics Education in Hacettepe University, Faculty of Medicine

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Abstract

Aim
In this study, our main goal is to emphasize the importance of medical ethics and its education. This study aims to discuss “how ethical education should be” by students by evaluating the results of the questionnaire.

Method
Questionnaire was used in order to reach our goals. This questionnaire which consists of three parts was prepared after a pre-study and literature search. The questionnaire was applied to 657 students.

Results
We collected the opinions of the doctor candidates on some topics by multiple choice case questions. Hereafter, there are findings and comments of their thoughts about the ethical education and their level of ethical knowledge and awareness. As result of our study, ethical knowledge and awareness of Hacettepe University Faculty of Medicine students are evaluated.

Conclusion
Students who filled the questionnaire are involved in the way of ethical awareness creation. Moreover, when our questionnaire results are evaluated well, it would be good source for development of ethical education.

Keywords
medical ethics education, ethical knowledge, ethical awareness, medical students

Introduction

Today, in the whole world scientific medicine is criticized more than ever and some negative feelings become widespread against medical doctors and employees of the health sector. Then what should be done in this situation? Since “everything is determined by its beginning”, starting from the student of medicine can be a good solution. The top priority of medical faculties should be educating medical doctors who are trained in consciousness of their professions' identity, communication and relationship with the others, well-equipped (not only technically and scientifically) in the ethics of our profession and sensitive about the public health problems.

The thing that the public expect from the doctor is not only to have a certain level of medical information and ability, but also to have some moral behaviors which are accepted as suitable to the identity of a doctor. Being interested in “human beings” requires a “virtuous” doctor. A doctor should exert a great effort to keep his scientific, professional, and personal characters above these expectations and continue with these characters. Faculties of medicine in which the art of being a doctor is taught is one of the most effective places where the identity of profession and ethical knowledge and awareness are acquired. From this point of view, medical ethics, medical humanities and human sciences in medicine get importance day by day.

In nature the universe of worthiness is formed by human. Ethics which is a branch of philosophy which examines this man-made universe of worthiness and make comments on what is good or what is bad, what is acceptable and what is not, what is right and what is wrong [1].

Nearly in all of the human ethics, there are serious problems about moral issues. There are also some problems behind the medicine which is a technical discipline about the morality of profession. Medical ethics analyzing the difficulties occurring during a medical activity makes use of some basic principles while criticizing and evaluating. Since the ethical problems are open ended by definition, those provide us a discussion platform rather than frameworks. Generally, even if it is accepted as there is no hierarchy between these principles. It is seen that in different situations different principles become important [1].

Some ethical violations observed in the history of medical ethics and still occurring today have an essential role in the location of today’s ethical issues and the establishment of the ethical committees. However, today these issues are still being debated and incoming ones are added [2]. Because we have a time period in which a clear change and development is observed in field of medicine as it happens in all branches of science [3]. New ethical concepts and contradictions will continue to come out as the medicine develops and people possess morality [4]. In order to solve these contradictions, doctors must internalize the ethical code and attitudes.

The criterion showing the internalization of the ethical codes and attitudes is the education of a doctor candidate [5]. Therefore, in this study, ethical education of the medical students from 1–5 phases in Hacettepe University is questioned and evaluation of the ethical knowledge and awareness of students is aimed.

In this study, the main goal is to emphasize the importance of medical ethics and its education. In the direction of this goal, ideas of the students of Hacettepe University Faculty of Medicine students are taken about some fundamental ethical problems, their education of ethics and the importance of ethical education. The thoughts about how this education should be and the place of student societies in education of ethics are observed.
One of the primary aims of this study is to discuss "how ethical education should be" by evaluating the outcomes of these questionnaire. In addition, measuring the level of ethical knowledge from the side of the patients' rights, basic principles and codes of medical ethics is among the goals of this study.

**Materials and Methods**

A questionnaire was used in order to reach our goals. This questionnaire which consists of three parts was prepared after a pre-study and literature search.

The first part is composed of multiple choice questions. The second part contains questions about level of ethical knowledge according to themselves, whether the education of medical ethics is necessary, how they got the knowledge of ethics, how ethical education should be and how a student society can contribute to the ethical education.

Finally, the third part aims to find out the students' awareness and knowledge about medical ethics. These questions are arranged according to the Likert type 5 degree scale as follows:

1—Absolutely disagree, 2—Disagree, 3—Not sure, 4—Agree, 5—Absolutely agree.

The respondents were from the phase 1–5 students of Hacettepe University Faculty of Medicine. The questionnaires were distributed by hand and collected at a center. The questionnaire was applied to 657 students. Fig. 1 shows that there is a well balanced distribution between the phases.

**Results**

In first part of the study, multiple choice case questions were asked in order to get the ideas of the doctor candidates about some topics. Hereafter, there are their thoughts about the ethical education, findings and comments about their level of ethical knowledge.

**Part 1. Multiple Choice Case Questions**

**Question 1:** A woman who has unstoppable bleeding and unconsciousness is carried to the hospital in which you are working as a gynecologist. It is understood that the patient has an ectopic pregnancy. You are thinking if you told the situation of the patient, who should be immediately operated, to her relatives, they could harm the patient since this is an illegal pregnancy. How would you behave?

a) The health and life of the patient is important for me. Therefore I wouldn't tell the truth to her family.
b) Since the patient is unconscious, relatives of the patient should decide on the operation. Therefore, I would tell the truth and get confirmation for the operation.
c) Although I think that it is not suitable to inform the relatives of the patient, I would give information to them in order to protect myself from legal problems that can occur in case of a complication.
d) My level is insufficient to decide on this.

In this case, we see that there is a conflict between the principle of not harming the patient and the principle of informed consent [6].

If we obey the principle of informed consent, we disobey the principle of not harming the patient. In addition, if we inform the relatives to get approval, we disobey the confidentiality rule. On the contrary, if doctor does not instruct the relatives he may face some legal problems.

40.9% of the students thought that even if it was not suitable to inform the relatives, it was necessary to instruct them in order not to face legal problems.

Principles of "not sharing patient's information—confidentiality", "benefit" and "informed consent" should be evaluated altogether in this case and 40.9% of the students preferred to inform relatives to protect themselves from the legal problems that may occur in the case of complications to not informing the relatives according to the principle of confidentiality and not harming.

26.9% of the students said that health and life of the patient was important. Therefore the family should not be informed (in this case, although the doctor may face some difficulties legally, he obeys the principle of confidentiality and the most important ethical principle is not harming the patient).

13.1% stated that since the patient was unconscious, the relatives should decide the operation, therefore, the truth must have been told them in order to get approval (they preferred the principle of informing to confidentiality).

11.6% students said that their level was insufficient to decide.

7.5% thought to follow a different way as "I would tell the family that the patient has bleeding and operation should be done immediately but I wouldn't say this bleeding is due to ectopic pregnancy."

**Question 2:** A 9 week pregnant woman comes to your clinic (clinic has a good technical equipment and health conditions) for her routine examination. Baby and the woman is healthy, and pregnancy is going well. However, however, the couple says that they want to terminate the pregnancy. How would you behave?

a) The will of the couple is important for me and since the legal period (10 week) is not over, I would terminate pregnancy.
b) principally, I am against the termination of pregnancy if both mother and baby are healthy. I would tell this to the couple and reject.

c) principally, I am against the termination of pregnancy if both mother and baby are healthy, however, when thinking about the possibility that the couple can terminate the pregnancy in an unhealthy environment, I would do what they want.

d) My level is insufficient to decide on this.

In a relationship in which there is respect to patient's values, a doctor may defend his/her values (but should not cause any harm on patients). The doctor has the right to abstention from the situation which does not fit his values and he should not be forced into this kind of applications [7].

When we evaluate the attitudes of the doctor against abortion, 37.4% of them stated that they were against the termination of pregnancy if both mother and baby were healthy. They would tell this to the couple and reject. Similarly 27.7% thought that they were against the termination of pregnancy if both mother and baby were healthy, however, when thinking about the possibility that the couple could terminate the pregnancy in an unhealthy environment, I would do what they want. 25.4% said that the will of the couple was important for me and since the legal period (10 week) was not over, I would terminate pregnancy. 5.7% stated that their level is insufficient to decide. 3.8% of students thought to follow a different way: "principally, I am against termination of pregnancy if both mother and baby are healthy, therefore, I direct the couple to another clinic which is safe."

**Question 3:** Doctor A recognized a tumor in the uterus of a woman who is 40 years old during the open gallbladder operation. By thinking that opening the patients body for another operation can cause the death if the patient, the doctor takes out the uterus of the patient. After this operation, no complications can be observed in the patient. However, the patient proceeds against the doctor by saying that she may want to have children in future. What do you think?

a) Doctor A is right. In this case the health and life of the patient is important.

b) Patient is right. The autonomy-right of decision making of the patient is violated.

c) My level is insufficient to decide on this.

Patient should decide after getting information about all the therapies. If she does not have the ability to decide, the relatives of the patient should be asked and their approval should be taken. If the patient does not have any relative, the doctor has two choices. The first one is to want protective people who are going to protect the autonomy of the patient from the court of law. This one is hard to apply and waste of time and generally these people want a doctor to make a decision. Alternative and the mostly used technique, especially in immediate decision required situations, the doctors should make the decision which he thinks that it will be true for the patient [8].

In the situation in which patients' autonomy is faced with benefit principle, 52.8% of the students thought that the patient was right. The autonomy-right of decision making of the patient was violated. (In this case, most of the students disagree with one of the most important principles of ethics-benefit.)

27% of students said that doctor A was right, in this case the health and life of the patient was important. 13.8% said that their level was insufficient to decide on this. 3.8% of students followed a different way as "during the operation, I would tell the situation to one of her relatives and after I get approval, I would take out the uterus" and "with high speed pathology techniques, tumor can be identified and decision can be made."

**Question 4:** In the neurology clinic in which you are working, one of your patients is diagnosed with the disease of a motor-neuron which does not affect the brain but in the course of a time it will paralyze all muscles. Your patient is afraid of pain which will be experienced in the last days of her life. Drug A you got can cease the pain of your patient, however, it is proved in the studies that this drug reduced life from 5 year to 3.5 year. How do you behave?

a) For me it is more important to prevent my patient's pain. I would drug my patient.

b) I wouldn't use drug. By thinking that I don't have right to reduce my patient's life.

c) I would explain situation to the patient and I would behave according to her decision.

d) My level is insufficient to decide on this.

The most important principle of medical ethics is benefit as providing patient continuity, disease treatment and pain prevention. A parallel principle is not harming [8]. The treatment of this situation is being discussed at two points. First one is the relation of benefit and harm that drug cause and second is the autonomy of patient [8].

When we take ideas of students about principles of benefit and not harming, 86.9% of students choose to explain the situation to patient and would behave according to the patients' decision.

5.4% said that I would not use the drug, by thinking that I didn't have right to reduce a patients' life anyway. 2.3% stated that for them it was more important to prevent their patient's pain. They would treat their patient.

4.6% of students said that their level was insufficient to decide on this.

0.9% thought to follow a different way such that "I would tell the situation to relative and take their ideas."

**Question 5:** A family who has five daughters wants to have a son after the pressure of family's elder members and community.

According to the law accepted by Israel government at 19.05. 2005, families having at least four children at same sex do have right to choose their next child's gender. How do you evaluate the application of the family?

a) Gender selection will spoil the equilibrium of nature and since "sex is not a disease" according to my thoughts, I would reject the will of families.

b) I would try to realize family's will in accordance with potentiality of medicine regarding the family's situation.

c) Since the aim of my profession is to gladden people, I would accept the family's will in any situation.

d) My level is insufficient to decide on this.
“Sex determination” is not regarded as appropriate in most of the countries in terms of ethics and law. Besides, in some countries like Israel, a different legal arrangement was done on this subject. However, in the country where this study is done “sex determination” is unethical and legally forbidden.

61.3% stated that gender selection will spoil the equilibrium of nature and since “sex is not a disease” according to their thoughts, they would reject the will of families. 24% signified that they would try to realize family’s will in accordance with potentiality of medicine regarding the family’s situation; 2.6% said that since the aim of their profession is to gladden people, they would accept the family’s will in any situation. 9.8% thought that their level is insufficient to decide on this. 2.3% of the students had unlikely thoughts. They said “If the laws and ethical committee approve this, I would accept patient’s will.”

**Question 6**: Y Company would like you to prescribe drug A, which is produced by Y Company, to while there exists an equivalent and cheaper drug B in the market. Drugs are tantamount in terms of patients. Cost or price difference is paid by government. How would you behave?

a) Offers of Y Company is not important for me. I would prescribe the equivalent cheaper drug. I don’t want to increase the financial load of the government.
b) I would decide on it with respect to the extent or size of Y Company’s offers.
c) I would directly accept their offer.
d) My level is insufficient to decide on this.

These kind of offers of the pharmaceutical industry, which doctors face so often, may be closely related with doctors’ ethical morality. Doctor should decide on the most appropriate drug considering many characteristics of drugs. While doing this, the point which should never be disregarded is the patients’ benefit, which is the basis of ethics concept. Financial load of the drug to the patient and government is one of the deterministic features of drug convenience as well as the effectiveness of the drug.

We got the answer “Offers of Y Company is not important for me. I would prescribe the equivalent cheaper drug. I don’t want to increase the financial load of the government.” from 88.4% of medical doctor candidates. 41% stated that they would decide on it with respect to the extent or size of Y Company’s offers and only 0.8% explained that they would directly accept their offer. 15% of students thought to follow a different way: “I would explain the situation to the patient and persuade him/her to use drug B.”

**Part 2. Ethics Education Related Questions**

In the first question of the second part of the questionnaire, the students were asked to assess their ethical knowledge level.

Evaluation according to phases is shown in Fig. 2.

When we evaluate the averages of the given answers separately in respect of phases, it is obviously seen that medical doctor candidates feel like having gradually insufficient level of ethical knowledge from phase 1 to phase 3. When compared to phase 3, phase 4 and 5 students’ level of ethical knowledge according to them is increasing again. According to us, the reason is that students recognize the variety of ethical problems through phase 3 and in phase 4 and 5, they feel satisfactory in struggling with ethical problems depending on their increasing clinical experiences.

When we asked students if education of medical ethics and bioethics should be involved in the educational program or not; we manifested that 95.2% stated that it was essential and 4.8% does not. Medical students’ accentuation to ethical education with such a high ratio is a really positive circumstance in terms of good medical practice.

By the second question, we aimed to find out how they have reached the current ethical knowledge level. As far as the overall evaluation is concerned, first place is taken by Good Medical Practice Program, second place is taken by books, movies and similar sources and third place is taken by courses.

“Good Medical Practice” (see Table 1), which is a part of medical curriculum of Hacettepe University, is a program basically designed on communication skills, supported and enriched by applications which include gaining professional and medical examination skills, discussing ethical and professional values, clinical visits (hospital, polyclinic), researches on medical humanities (history, law, philosophy, art etc.), clinical decision making and evidence based medicine [9].

In these sessions different phenomena, scenes from movies, articles from newspapers, decisions of ethics and honor committee are discussed and students prepare projects on certain topics [10].

This program was selected as the most important source for gaining ethical knowledge analogously by the phase 1, 2 and 3 students. Books, movies and similar sources took the second and courses took the third place. In phase 4 and 5 students, there exists a different order such as courses, master-apprentice
Table 1. Content of the “good medical practice” courses at Hacettepe University during the first three phases

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
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<tbody>
<tr>
<td>Health &amp; disease concept</td>
<td>Informed consent</td>
<td>Clinical ethics</td>
</tr>
<tr>
<td>Community’s health systems</td>
<td>Reliability</td>
<td>Research ethics</td>
</tr>
<tr>
<td>Patient rights</td>
<td>Dying patients and their relatives</td>
<td>Publication ethics</td>
</tr>
<tr>
<td>Expectations from doctors and students</td>
<td>Telling the truth</td>
<td>Alternative treatments</td>
</tr>
<tr>
<td>Benevolence</td>
<td>Keeping secrets</td>
<td>Inadequate sources</td>
</tr>
<tr>
<td>Rejection of treatment</td>
<td>Euthanasia</td>
<td>Reproduction technologies</td>
</tr>
<tr>
<td>Termination of doctor-patient relationship</td>
<td></td>
<td>Genetic tests</td>
</tr>
</tbody>
</table>

relation, books, movies and similar sources. The reason of this difference may be because Good Medical Practice is just in its third year and it is annually renewed by student feedbacks.

In the third question, they were asked to choose the best methods for ethics education. According to general evaluation: it is seen that first place is taken by small group discussions, second place is taken by courses and third place is taken by elective courses. The other offers or proposals from students are as follows: books, case discussions, master-apprentice relation, seminars, examples given by instructors within courses, participation of interns in committee discussions. In addition to these, ethics discussion near patients in routine visiting program is another ethical education method which is currently discussed.

In the last question, they were asked to choose the most appropriate activities by which student organisations could contribute to ethics education. According to general evaluation; order is as follows: Discussions, Movie shows, Seminars, National and International meetings, Projects. Another activity proposed by students is theater sketches/role plays.


Ethical knowledge level of students is displayed by assessment of the students’ responses to statements according to the current ethical principles (see Table 2) [12, 13].

The statements, except those numbered 6, 8, 10, 14, 16 and 18, are ethically correct, thus the students who marked “4” or “5” are regarded “informed/aware”, “3” are “hesitant”, “1” or “2” are “uninformed/unaware”. Contrary recognitions are applied to the rest.

When we evaluate the data regarding these informational questions (statements), it came out that most of the questions (17 out of 20) are responded correctly at high ratios over 60% of the students. However, other three questions seem to confuse the mind (number 6, 8 and 18).

The 6th statement is regarded as “wrong” by only 13.0% of the students, who seem to be more aware than the others. 65.9% of the students think that “technical-physical impossibilities affect ethical responsibilities of the doctor”. In fact, ethical values should be embraced as principles and rules unconditionally. If

Table 2. Questionnaire on the level knowledge and awareness of ethical subjects

<p>| | |</p>
<table>
<thead>
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<tbody>
<tr>
<td>1</td>
<td>Possible medical results if not treated should be explained to the patient</td>
</tr>
<tr>
<td>2</td>
<td>Patients have the right to ask for medical records</td>
</tr>
<tr>
<td>3</td>
<td>Risks of medical treatment and intervention should be explained to the patient</td>
</tr>
<tr>
<td>4</td>
<td>Patients’ autonomy is as important as medical assistance s/he will acquire</td>
</tr>
<tr>
<td>5</td>
<td>Doctor should explain both the scientific and public name of the disease to the patient</td>
</tr>
<tr>
<td>6</td>
<td>Technical-physical impossibilities affect ethical responsibilities of the doctor</td>
</tr>
<tr>
<td>7</td>
<td>Doctor should let some time to patient to decide on medical treatment</td>
</tr>
<tr>
<td>8</td>
<td>As the patient does not have medical information, doctor can make medical decision for patient</td>
</tr>
<tr>
<td>9</td>
<td>Patient who is involved in medical decision should be completely capable of deciding</td>
</tr>
<tr>
<td>10</td>
<td>In fatal diseases, medical fact should be kept from patient</td>
</tr>
<tr>
<td>11</td>
<td>In organ transplantation, “justice principle” should be considered</td>
</tr>
<tr>
<td>12</td>
<td>Defending patient rights is a responsibility of doctor</td>
</tr>
<tr>
<td>13</td>
<td>Patient has the right to determine another person to decide for him/herself</td>
</tr>
<tr>
<td>14</td>
<td>Identity of patients who will participate in a research could be published</td>
</tr>
<tr>
<td>15</td>
<td>Patients have the right to reject participating in a research</td>
</tr>
<tr>
<td>16</td>
<td>Computer records belonging to the patient should be available for others</td>
</tr>
<tr>
<td>17</td>
<td>During the period of treatment, patients also have important responsibilities</td>
</tr>
<tr>
<td>18</td>
<td>Doctors are free to reject their patients</td>
</tr>
<tr>
<td>19</td>
<td>Use of patient’s material in researches depends on patient’s permission</td>
</tr>
<tr>
<td>20</td>
<td>Medical decision should be made by both doctor and patient in common</td>
</tr>
</tbody>
</table>

1: Absolutely disagree; 2: Disagree; 3: Not sure; 4: Agree; 5: Absolutely agree
they are accepted, they are present in all circumstances. Any reasons such as technical or physical deficiencies cannot be a justification to neglect ethical values [11].

While the 8th statement is regarded as “wrong” by 29.2% of the students, “hesitant”s are 35.5% and those who believe that doctors can make decision instead of the patient are not less: 35.3%. This statement is in the direction of act of informed consent and principle of respect to patient autonomy related to necessity of patient’s participation in medical decision. Every medical student would be expected to disagree with this statement. But this surprising result may have occurred due to deficient ethical information about patient autonomy.

We observe a variance among the given responses to the 18th question as well as the 8th question. The rate of those who think that doctors are free to reject their patients is 39.4%; 29.8% of students are hesitant, and 30.8% of them disagree with the statement. Rejection of a patient by a doctor may only happen in some exceptional circumstances, but we cannot talk about a boundless freedom of rejection. Under such exceptional circumstances, the physician may discontinue the professional relationship by notifying the patient and, with the approval of the patient, transfer to another physician the information in the record, provided that adequate care is available elsewhere and the patient’s health is not jeopardized in the process [12].

According to the responses to these informational questions, each phase’s average score was also checked. The resulting data is shown in Fig. 3.

The obtained result regarding average knowledge level of phases is not parallel with our expectations. Our prudence were in direction of increasing level of ethical education from phase 1 to 5. However, although we face the highest values in phase 4 and 5 students, phase 2 has higher score than phase 1 and 3. This contradiction may have occurred due to Good Medical Practice program, ethics courses, clinical ethics applications or apathy to the survey.

Discussion

Today, people know much more of what others are doing, and since resources are getting scarcer, the necessity of establishing co-operation on grounds of honesty is increasing. For this reason, and simply because relationships and activities among people are on a global scale, we have to establish a common normative basis on which we can agree. In order to do this, we need the help of ethics in the discipline of medicine. The pre-condition for medical ethics to fulfill this duty is to recognize the norms and values that are accepted, respected and approved in practice by other cultures; to examine these components in terms of their functions, which guide and regulating practices and activities in general; and to explore to what extent they are able to be acceptable in global terms. In an era in which economics and technology determine everything that happens all over the world, medical ethics has to lead by warning of the destructive effects and outcomes of an insincere utilitarian attitude that tends to “rationalize” the world of medicine. The world of medicine can become abstract if it is based purely on benefit and success. Medical ethics therefore reminds us that there is a source of aims and objectives that is based on ethical perfection of practical wisdom; that there are “qualitative values” that do not fit into the “quantitative values” of respect for patient autonomy, beneficence, honesty, justice, etc.

In this concept as result of our study, ethical knowledge and awareness of Hacettepe University Faculty of Medicine students are evaluated. Besides, we have taken a step forward in the way of creating ethical awareness of students who filled the questionnaire. Moreover, when our questionnaire results are evaluated well, it would be a good source for development of ethical education.

Multiple Choice Case Questions

When the case questions are studied “My level is insufficient to decide on this” answer’s ratio is fluctuating from one to another. 13.8% for question 3, 11.6% for question 1 and 9.8% for question 5. 3rd question is the most difficult one to answer by students. This result shows us students’ low level of knowledge and awareness among the topics: “patient autonomy”, “share of patient information—confidentiality” and “sex determination”. In educational programs, this and related issues should be included more.

1. Most of the students have preferred “informed consent” principle instead of “confidentiality” and “beneficence” principles.
2. According to approximately one third of the students, abortion is not ethical.
3. Most of the students stated that beneficence principle can be disregarded while the patient’s “autonomy” is considered.
4. Approximately all of the students indicated that they would present a respectful attitude to patient’s autonomy.
5. More than half of the students do not support sex determination.
6. Answer to question about doctor-industry relationship is surprising. 41% of the future doctors stated that they would decide on it with respect to the extent or size of pharmaceutical company’s offers and only 0.8% explained that they would directly accept their offer. These low ratios help us to stipulate that doctor-industry relationship will not reach to the level at which the ethical concepts will be violated.

Medical Ethics Education

Medical doctors’ and doctor candidates’ should be educated on doctor identity, communication skills, talking to patients, recog-
nizing certain behaviors and skills. Then, how should be the education of medical ethics performed in medical faculty for the doctors of future? This education can be given at undergraduate level in medical faculty in the scope of History of Medicine–Deontology–Medical Ethics courses and in the scope of continuing medical education at postgraduate level, especially to clinicians. In the example of “master–apprentice relation” in clinics, instructor, who will be “role-model” to the students, should pay attention to his/her behavior and attitude towards patients [14].

It is seen that the ‘Good Medical Practice Program’ has influenced the participated students’ ideas about ethical education and level of ethical knowledge and awareness. Since it is a new phenomenon to make this program institutional and widespread, students who have just begun their study are luckier. According to the results, we manifested our ideas about medical ethics.

Core Committee of International Institute of Medical Education, which was established in 1999 for medical education, accepts the item “professional values, attitudes, behavior and ethics” among the “minimum learning outputs” which is designed for all students graduating from faculty of medicine for the entire world [15]. The place of ethical education in medical education can be strengthened and reinforced by Good Medical Practice or similar programs, sources like books and movies and studies of student organizations.

**Ethical Knowledge and Awareness Level**

It came out that most of the medical students at Hacettepe University, have accurate information about ethical values. However, some challenging issues of medical ethics continue confusing the mind. Therefore, we should raise awareness of medical students in a broader manner.

**Recommendations**

We have reached quantitative outcomes at the end of our study. However, in the third part of our study, restrictions of the questionnaire application, the possibility of answers, which does not reflect the reality but reflects the expected, generates the deficient point of our study. These deficient points can be corrected by supporting with different methods.

In all fields of ethics, wide ranged studies can be applied by selecting various cases.

International health programs can be beneficial for students to recognize how health is perceived, what kind of problems occur and how solutions are found to these problems in other parts of the world that is similar to or different from their own countries [16]. By this way, the discussions about the ethical education can be performed in the international platforms. Recurrence of our study in Europe or other countries in the world would guide these kinds of discussions.

**Acknowledgement**

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Richard Schol
JEMSA Editor

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Fig. 1 Webpage www.uptodate.com.
Scientific Biomedical Student Congresses in Europe

Floris Imhann
Secretary of the 14th ISCOMS, The Netherlands

Students: Present Your Research Infront of an Audience!
After working vigorously on your rt-PCRs, your SPSS-database or immune-histochemistry dyes for months, you can write an essay and leave it at that. You can also show the world what you have done.

The International Student Congress of Medical Sciences in Groningen (The Netherlands) is one of the student congresses in Europe that offers a venue for those who want to present their biomedical research projects. More-over the ISCOMS investigates the use of presenting science and provides students with some lecture-skills.

Improve Your Career
Does presenting research projects really makes a difference for your future career? The ISCOMS organisation wondered if presenting at a scientific student congress is actually beneficial for students and their future career.

In 2002, a retrospective study was done to investigate whether students who presented their research projects had published more articles. A group of 81 Dutch ISCOMS-presenters in 1995 and 1997 was matched to a group of 81 Dutch non-presenters and their scientific output until 2002 was scored. The main result: Students who presented at the ISCOMS had published four times more papers than non-presenters, showing the importance of student congresses. This encourages the ISCOMS in helping students prepare themselves for congresses.

Learn to Present
How to keep the attention of a crowd and how to explain something difficult and very specific to a diverse audience varying from first year medical students to a jury of professors? Because presenting research is a difficult but valuable skill which can mainly be learned by doing so, the ISCOMS organizes two Master classes on how to present a research project. Two experienced professors teach how to hold a poster or oral presentation. Of course, the real lesson is the presentation at a congress itself.

Science is Not All There Is
Fortunately, student congresses are not merely scientific. Most congresses have an extensive social programme where participants meet and complete the experience in a relaxing way.

So improve your career, learn to present and have a great time at the ISCOMS or one of Europe’s other biomedical student congresses. More information about the ISCOMS as well as a list of other student congresses can be found on www.iscoms.nl.

Congress Organizations:
Focus on Cooperation in Talent Scouting!
Scientific congresses for biomedical students sprout up rapidly in Europe. These congresses should cooperate in order to help talented medical students find research projects around Europe.

Because most scientific student congresses are also a competition, these platforms form excellent opportunities to scout talented young researchers. When gifted European medical students are able to participate in projects all over Europe they can form the new, more mobile, generation of researchers and meet EU goals set for mobility and science.

Local Initiatives
Already some great local projects are organized by student congresses. One example is the one-year fellowship of the European Student Conference in Berlin (ESC) where a student, after a strict application procedure during the congress, could come back to Berlin and finish for example his or her scientific rotation.

The ISCOMS has prepared its fellowship programme (IRF) for the third year. Sixteen talented students who applied for a project will be invited to stay after the congress in June 2007 and work for two weeks on a project in their field of interest.

Already two former IRF-participants are now PhD-students in Groningen, The Netherlands, showing that the talent-scouting works. Subsequently the ISCOMS together with our partners in Groningen and Mannheim (Germany) also prepares a programme of lab courses where students get acquainted with new techniques.

Alliances
When student congresses not sheerly compete, but build more alliances and create initiatives to exchange talented students, the congresses, the universities and the students will benefit.

An important start has been made at the EMSA National Coordinators Meeting 2007 where ISCOMS, ESC and EMSA founded the Network of European Medical Student Congresses (NEMSC). One of its main goals is to exchange talented student researchers.

This promising initiative could be the first step towards increased mobility among medical students. The NEMSC website will be created in the near future.

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THE HEART BEYOND THE ANATOMY

This is the year’s main topic of the 18th European Students’ Conference (ESC), which will take place from the 7th to the 11th of October 2007 at the Charité Universitätsmedizin Berlin.

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The ESC offers an attractive programme to passive participants. Keynote lectures, lecture courses, panel discussions or workshops held by internationally distinguished guests of the topic “Cardiovascular System”. The Highlights are going to be lectures about the up-to-date topics as Alternative Medicine, Ocucchmophatology and Cholesterol, Metabolic System, Adiposity, Hypertension, Spacemedicine and an interdisciplinary course lecture about “What is love?”.

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Monoclonal Antibodies in Angiogenesis Inhibition—Bevacizumab and Vitaxin to Fight Cancer

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Abstract

One of the possible ways to inhibit development of a tumor is blocking the growth of new blood vessels that provide oxygen and nutrients to the malignant cells. A new approach is to use the high specificity of monoclonal antibodies to target essential angiogenic molecules. These antibodies are derived from cell lines consisting of identical clones, and recognize the same part of a macromolecule. The most relevant are bevacizumab and vitaxin. The first one is approved for first-line treatment of metastatic colorectal cancer, whereas vitaxin is still in clinical trials. Preliminary results are optimistic, and the drugs are generally well tolerated by patients.

Keywords
neovascularization; monoclonal antibodies; vascular endothelial growth factor A; integrins; cells; therapy

Finding efficient therapeutic methods for cancer patients is one of the most important and most difficult goals in modern medicine. The main problem is the low specificity of destructive drugs—it is necessary to discover drugs that will selectively ablate the mutated proliferating cells without significant damage to the normal cells. One possible instrument for specific attack is a monoclonal antibody, and a possible way to destroy a tumor is to block its nutrition source—the angiogenesis. Research is now concentrating to stop angiogenesis, and one of the most specific and most promising methods is the use of monoclonal antibodies.

Angiogenesis—the Creation of New Blood Vessels

The growth of new blood vessels includes multiple complex processes such as endothelial proliferation, migration, differentiation and degradation of the extracellular matrix, and is a normal physiological event [16, 18]. It is induced by hypoxia and involved in events during embryonal development, tissue remodeling or wound healing, and could therefore have therapeutic uses in tissue repair and regeneration [1, 11, 25, 35]. However, the development of new vessels is also important in tumor growth where it is essential for the delivery of nutrients and oxygen to the tumor mass and, in that way, for its survival. If we want to block this neovascularization, we must first understand the fundamental factors that trigger and control this process, so that we can precisely influence it.

During hypoxia, the hypoxia inducible factor (HIF-1) is being activated, which is actually a transcription factor, leading to increased transcription of a number of genes [16, 35]. The most important product is the vascular endothelial growth factor (VEGF), a strong mitogen. It subsequently induces proliferation and permeabilization of endothelial cells, starting in that way the formation of new capillaries. The mechanism of induction is binding of VEGF to its receptors VEGFR1 and VEGFR2 (tyrosine kinases), expressed on endothelial cells, and activating thereby a signaling pathway in the cells [36]. But the process is more complex, and we know that except HIF-1 there are multiple other factors facilitating VEGF expression, including transforming growth factor \( \beta \) (TGF\( \beta \)), fibroblast growth factor (FGF), and platelet-derived endothelial growth factor (PD-EGF) [16, 23, 31]. Tumor angiogenesis is induced both by oncogene-driven expression of these pro-angiogenic factors as well as by hypoxic conditions. The endothelial cells that are growing into a tumor mass express proteins that are not normally present on their surface (or not significantly), like \( \alpha_\beta \) integrin and receptors for angiogenic growth factors [18]. They use the integrins (cell adhesion receptors) to interact with extracellular matrix proteins, what is necessary for their migration [15]. Generally, all of these factors and signaling steps could be targets for specific anti-tumor therapies.

Inhibition by Monoclonal Antibodies

Theoretically, there are many possible ways of inhibiting angiogenesis, and some of them are already being used [23]. Direct inhibitors prevent vascular endothelial cells from proliferating, migrating or avoiding cell death in response to pro-angiogenic proteins. Indirect inhibitors, on the other hand, prevent the expression or block the activity of a tumor protein that activates angiogenesis, or block the expression of its receptor on endothelial cells [23]. The use of monoclonal antibodies opens the possibility of high specific influence, due to their special characteristics.

In contrast to impure mixtures of polyclonal antibodies, which are derived from multiple different cells and thus react with a number of different epitopes (specific parts of macromolecules that are recognized by antibodies), monoclonal antibodies are produced by immortal cell lines that consist of identical clones. All of these cells produce the same antibody, which recognizes one epitope [2]. The cell lines are derived from multiple myeloma (type of cancer), a malignant disorder of antibody-producing cells, by fusing a myeloma cell with a short-lived antibody-producing cell. The resulting immortal hybrids are called hybridoma cells. Each of them indefinitely produces homogeneous antibody specified by the parent cell. And how can we control the specificity of the antibody? By injection of the desired target protein into an animal (mouse, for example) and removing its spleen after the immune system is activated. The short-lived antibody-producing cells can then be isolated from the spleen and used to create hybridomas [2]. Because the antibodies obtained from animals are often recognized as foreign by the patients, leading to human anti-mouse antibody responses, modern molecular techniques were developed to create humanized antibodies. These antibodies have only a small region of foreign origin (a part of the antigen recognition site), whereas the rest is replaced by its human counterpart [40].
Two monoclonal antibodies are today being extensively evaluated as drugs that inhibit angiogenesis. The first is bevacizumab, a humanized antibody against vascular endothelial growth factor (VEGF)(8), and the second is vitaxin, a humanized antibody to the α4β1 integrin [15]. A third one, volociximab (M200), is specific to the αvβ3 integrin, and is at the beginning of its therapeutic valuation [33].

**Treatment with Bevacizumab**

Bevacizumab (Avastin) is the first angiogenesis inhibiting monoclonal antibody approved by the US Food and Drug Administration (FDA), targeting VEGF and thereby preventing its interaction with the VEGF receptor tyrosine kinases VEGFR1 and VEGFR2 on endothelial cells [8] Experiments indicated that tumor cells also express these receptors [10], what means that bevacizumab could have a direct effect on them as well. Treatment regimens being examined include bevacizumab alone and in combination with various different approaches including conventional cytostatic chemotherapy, radiation, immune therapy and biologically targeted agents [5] Preclinical models showed angiostatic effects in combinations with other methods, but even single-agent therapy resulted in tumor growth inhibition of 20 different human tumor cell lines (13 tumor types) implanted into mice [12]. Although bevacizumab is able to bind human Fc receptors and complement, it does not demonstrate cell or complement-mediated cytotoxicity in both VEGF producing or targeting cells, probably because VEGF is not a cell-based target [41].

Clinical trials first showed good results in treating metastatic colorectal carcinoma. Bevacizumab was studied in combination with 5-fluorouracil-based chemotherapy and showed significant prolongation of survival, after what it was approved for the first-line treatment of this disease [8] Direct evidence exists that even a single infusion of bevacizumab decreases tumor perfusion, interstitial fluid pressure, vascular volume and density, and the number of viable, circulating endothelial and progenitor cells in rectal cancer patients [42] The decreased interstitial fluid pressure facilitates the delivery of other chemotherapeutic drugs to the tumor, what could be one of the reasons for synergistic antitumor activity [12]. There also is preliminary evidence of efficacy for breast, non-small-cell lung, pancreatic, ovarian, cervical, prostate, head and neck and renal cancer as well as haematological malignancies [6, 34, 43] Some recent experience in treatment of malignant effusion in cancer patients indicates activity of high doses of bevacizumab [32]. It is interesting to note that an analysis of the mutation status of genes like ras, raf or p53 in patients treated with bevacizumab [20] did not show that this mutations had any clinical relevance to the efficacy of the therapy (unlike previously assumed). That is, all subgroups benefited from the addition of bevacizumab to standard chemotherapy, regardless of the status of those markers.

**Side Effects and Adverse Reactions of Bevacizumab**

In comparison with traditional cytotoxic drugs, bevacizumab was generally well tolerated by the patients in the clinical trials. However, some unusual toxicities were noted to be associated with bevacizumab: gastrointestinal perforations, wound healing complications, hypertension, thromboembolic complications, bleeding and proteinuria [4, 29]. An increased risk of severe bowel complications (including ischemic colitis and gastrointestinal perforation) was also described in patients treated with bevacizumab who have undergone previous radiotherapy [26]. A nasal septum perforation induced with bevacizumab has been reported, probably due to negative effects of the drug on neovascularization in wound healing [9]. One of the numerous described thrombotic events is a recent example of a left intracardiac thrombotic mass, leading to life-threatening arrhythmia and ventricular systolic dysfunction [37]. The apparent contradiction of increased risk of both bleeding and thrombosis could theoretically be explained by two mechanisms. A decreased reperfusion capacity of endothelial cells in response to trauma, as a result of VEGF antagonism, is suggested to be the reason for bleeding tendency, whereas thrombotic events could be a consequence of endothelial disfunction and exposure to subendothelial collagen [24]. In a recent case report a scin rash (red papillary nodules on the chest, back, forehead and around the eyes) has been linked to bevacizumab administration in a patient
with colorectal carcinoma, who had a positive response to treatment [13]. While some studies report successful therapy of colorectal liver metastases, without severe surgical, wound-healing or bleeding complications [14], others claim that there is an increased risk, describing portal vein thrombosis and hepatic steatosis after preoperative bevacizumab treatment [7]. It seems, therefore, that although bevacizumab is obviously very helpful in cancer therapy and relatively good tolerated by the patients, its toxicities and increased risk of adverse effects need to be further investigated.

Except in cancer treatment, the use of bevacizumab is also possible in other conditions that include neovascularization, such as in treatment of atherosclerotic plaque [39] or ophthalmologic problems [22, 38].

Studies of Vitaxin

Another possible tactical point for blocking angiogenesis is, as previously stated, the interaction between cell integrins and proteins from the extracellular matrix [21], because this interaction is probably necessary for endothelial cell migration and prevention of apoptosis (cell death), and thereby tumor growth and metastasis. Vitaxin is an antibody specific to α5β3 integrin, a protein not significantly upregulated on normal endothelium. This fact allows us to expect a possible selective influence on the tumor growth, without severe side effects. The purpose of the antibody is not only to block this interaction between integrins and matrix proteins, but also to inhibit signal transduction [21] that leads to cell migration, the mechanisms of which are not yet fully elucidated.

Vitaxin (MEDI-522) is still in clinical trials. Preclinical investigations confirmed the induction of apoptosis of proliferating vascular cells and the rapid regression of distinct tumor types transplanted onto the chick chorioallantoic membrane [3], as well as inhibition of tumor development in mouse models of human melanoma [28]. First studies on patients with various metastatic cancers refractory to standard therapy demonstrated clinical benefit after infusions of the drug for several weeks [15]. Some patients demonstrated disease stabilization or partial response, including a patient with partial tumor response maintained for 22 months. The doses were chosen to produce plasma concentrations to saturate the α5β3 integrin in vitro. On the other hand, in a study on patients with advanced leiomyosarcomas no objective response or stabilization of disease was noted [30]. The authors stated that suboptimal dose and schedule, as well as the advanced nature of the disease in these patients, could be possible explanations for the failure. A recent report suggested clinical activity in metastatic renal cell cancer and an effect on tumor perfusion [27]. There are also preliminary results of efficacy in treatment of metastatic melanoma, published on meetings of the American Society of Clinical Oncology [17].

Side Effects and Adverse Reactions of Vitaxin

The therapy with vitaxin was well tolerated with little or no toxicity [15, 17, 27, 30]. The major adverse events observed were inf

Alternative Explanation of Working Mechanism

Some interesting experiments indicated that the true mechanism of how vitaxin inhibits angiogenesis is somewhat different than previously assumed. Genetic ablations of the genes encoding α5β3 and αβ1 failed to block angiogenesis in experimental models, and in some cases even enhanced it [19]. This led to the hypothesis that these integrins are negative regulators of angiogenesis, and that vitaxin and other drugs targeting them may be acting as agonists, rather than antagonists. Anyway, the fact is that our understanding of the details of angiogenesis and its inhibition is incomplete and that further research is required.

To conclude, the production of monoclonal antibodies targeting specific processes in tumor development has opened new perspectives in oncoligic therapy. By manipulating angiogenesis, scientists hope to find ways to block the growth of a tumor mass and to reduce it, without causing serious side effects. In this regard, the combination of anti-angiogenic with surgical and other treatments could represent an efficient method for successful fighting against this disease. Antibodies, while still at the beginning of their use, displayed great potential for the future. However, there is much to learn about how they influence both tumor survival and normal body functions, before we can make a definitive evaluation of their performance. The use of monoclonal antibodies is nevertheless promising, including those that exist today, but also those yet to be designed.

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Abbreviations
VEGF  Endothelial Growth Factor
VEGFR1  Endothelial growth factor Receptor 1
VEGFR2  Endothelial Growth Factor Receptor 2
HIF-1  Hypoxia Inducible Factor 1
TGFβ  Transforming Growth Factor β
PDEGF  Platelet-Derived Endothelial Growth Factor
FGF  Fibroblast Growth Factor

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Circulating Acetylcholine Revisited: Physiological and Clinical Relevance

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Abstract

Acetylcholine is generally known in medical areas as one of the most exemplary neurotransmitters, yet its ubiquity in nature suggests a theoretically much more diverse spectrum of action, and an extremely early appearance in the evolutionary process.

In humans, acetylcholine and/or the synthesizing enzyme, choline acetyltransferase, have been found in an array of non-neural tissues: epithelium, mesothelium, endothelium, muscle, immune cells and, at last, blood cells. The widespread expression of non-neuronal acetylcholine is accompanied by the ubiquitous presence of acetylcholinesterase and nicotinic/muscarinic receptors. Structural and functional dissimilarities are evident between the non-neuronal and neuronal cholinergic systems. Over the past years a striking body of evidence has been gathered, indicating that acetylcholine additionally consists of a cellular signalling molecule.

A progressively rise of knowledge asserts that numerous erythrocyte physiological events are strongly regulated by acetylcholine. It modulates (i) the red cell rheology; (ii) plasma ions concentrations; (iii) nitric oxide intracellular translocation and metabolism; (iv) apoptosis.

Per se, it is time to revise the role of acetylcholine in humans. Its biological and pathobiological roles must be evaluated in more detail and, possibly, novel therapeutic targets might become reachable.

Keywords

Acetylcholine, acetylcholinesterase, erythrocyte, nitric oxide, non-neuronal cholinergic system, rheology, vascular disease.

Profile

As part of the overall doctors’ commonsense, acetylcholine (ACh) acts as a neurotransmitter inside the central and peripheral nervous systems in human beings. However, recent experiments in humans demonstrate a widespread expression of the cholinergic system within varied non-neuronal tissues.

“Non-neuronal Cholinergic System” (NNCS) is a novel notion that regards the extra-neural effects of acetylcholine. It is becoming progressively evident that the cholinergic system is not confined to the nervous system, yet being nearly ubiquitous. Acetylcholine is far from being exclusively a neurotransmitter, acting to mediate rapid communication between neurons and effector cells. It has been shown to occur in human blood circulation, being produced by T-lymphocytes and vascular endothelium. An interesting finding concerns the enhanced levels of circulating acetylcholine seen in certain inflammatory diseases; for instance the 14-fold higher content of ACh verified in patients with atopic dermatitis, along with the anti-inflammatory effect of ACh in the rat’s systemic response to endotoxin.

The biology of the NNCS in humans has been recognized in the past. For instance, vascular endothelial cells together with immune cells (namely lymphocytes) express the whole components of the cholinergic system independent of any neural innervation. The emergence of this new job for ACh becomes a way to further optimize the cholinergic action for its additional neural role. The synthesis and function of acetylcholine in the non-neuronal system (e.g. blood cells) has been object of many investigations taking into account its vascular action (see Fig. 1).

The leading tasks for the decades to come will be to dissect the multi-biological role of non-neuronal acetylcholine in detail and to identify pathological conditions in which this system is up- or down-regulated. This issue could provide the basis for the development of further therapeutic weapons to target the NNCS.

Fig. 1 Circulating acetylcholine as a broad vascular modulator.
This article will primarily focus on the expression and function of the NNCS in human red blood cells and possible therapeutical implications.

Non-Neuronal Acetylcholine—A locally acting molecule

The cholinergic system, both neuronal and non-neuronal, consists of the synthesizing enzyme choline-acetyltransferase (ChAT), the signalling molecule acetylcholine, storing organelles (cholinergic vesicles and transporter proteins), Ach-sensitive nicotinic and muscarinic receptors and the hydrolysing enzymes, i.e. the specific acetylcholinesterase (AChE) and non-specific cholinesterase (pseudocholinesterase, butyrylcholinesterase or plasmaacolinesterase) [1–4].

Acetylcholine, being composed of the three most common atoms (carbon, nitrogen, and oxygen), represents a phylogenetically old signalling compound. Since that “ancient time”, acetylcholine, say, the overall cholinergic system, has been used in the evolutionary process both in plant and animal kingdoms, especially humans [2]. One may hypothesize that this purported evolutionary process has optimized the cholinergic system possibly to utilize acetylcholine as an intracellular signalling molecule, to utilize acetylcholine through either auto or paracrine behaviours, and at length, to use it as a neurotransmitter. Considering this, it is not surprising to find that the vast majority of human cells contains ACh, such as epithelial, mesothelial and endothelial cells, circulating cells and immune cells. The stockpile, transport, and release of ACh seem to differ between neuronal and non-neuronal cells. Throughout time, variable regulations of acetylcholine synthesis in all the different cells have been achieved by creating ChAT isoenzymes [1–2]. Yet, the number of distinct isoenzymes expressed in human tissues remains to be elucidated.

The action of ACh is prevented by inactivating enzymes, predominantly the specific acetylcholinesterase and the non-specific butyrylcholinesterase (BChE). The ubiquitous expression of these cholinesterases’ activity guarantees a functional division between the molecule’s dual job—the local hormone/modulator and the neurotransmitter. Non-neuronal acetylcholine appears to be involved in the regulation of elementary cell functions such as cell mitosis, cell-cell interaction, cell automaticity, locomotion, ciliary activity, barrier function, resorption and secretion [3]. In addition, immune cells appear to be regulated by the cholinergic system as well. For example, the excitability of airway mast cells can be powerfully inhibited by acetylcholine.

Non-Neuronal Acetylcholine—Widely distributed in biological systems

Either ChAT or ACh have been described to occur roughly in all epithelial surface cells (goblet cells, ciliated cells, basal cells), submucosal glands and airway smooth muscle fibres. Acetylcholine is also demonstrated in effector cells of the immune system (lymphocytes, macrophages, mast cells). Epithelial, endothelial and immune cells are additionally endowed with nicotinic and muscarinic receptors. Thus, the cytomolecule acetylcholine can contribute to the regulation of basic cell functions via auto-/paracrine mechanisms described above (proliferation, differentiation, secretion of water, ions and mucus, cytoskeleton organization). Acetylcholine also modulates immune functions: release of cytokines, proliferation, cell activation and inhibition. Regarding to the cholinesterases, red blood cells are the blood elements heaviest packed with AChE, whereas BChE is uniformly spread in the liver, lung, smooth muscle and into the bloodstream [3–4].

In this scenario, this cholinergic pitfall comes up as an unapparent source of crucial cellular effects that ACh itself carries out (see Table 1).

For decades, a substantial increase of ACh tissue content in chronic inflammatory diseases has been reported, along with increased clonal expansion of the immune system. Beyond the well-known concept of the “inflammatory reflex” [5–6], which reports a reduction of acute inflammatory states after vagus-stimulation, the (non-neural) inflammatory role for ACh is not well understood. In the airway, for instance, the great majority of cells express the components of NNCS and it is documented that a substantial increase on ACh levels triggers the release of proinflammatory effectors [7].

Finally, detailed analysis of the expression and function of non-neuronal acetylcholine may help to gain more knowledge of the pathogenesis of chronic inflammatory pathology of mucosal and skin tissue. The NNCS may be involved in the pathogenesis of chronic inflammatory mucosal diseases, including allergy-related pathology [7]. Up-regulated epithelial acetylcholine may cause an impairment of the barrier and immune functions. It will be a major goal for further research to identify the physiopathological conditions in which the system is up- or down-regulated. Additionally, innovative compounds, targeting the expression and function of the NNCS by topical application (for

| Table 1 Human tissues in which non-neuronal acetylcholine has been identified [4] |
|------------------|------------------|
| **Epithelial Cells** | **Endothelial cells** |
| Airway | Pulmonary vessels |
| Urogenital tract | Liver, thyroid gland |
| **Glandular tissue** | **Immune cells** |
| Female breast, glandular acini | Lymphocytes, alveolar macrophages |
| **Non-Neural Cholinergic Systems—Widely distributed in biological systems** |

Either ChAT or ACh have been described to occur roughly in all epithelial surface cells (goblet cells, ciliated cells, basal cells), submucosal glands and airway smooth muscle fibres. Acetylcholine is also demonstrated in effector cells of the immune system (lymphocytes, macrophages, mast cells). Epithelial, endothelial and immune cells are additionally endowed with nicotinic and muscarinic receptors. Thus, the cytomolecule acetylcholine can contribute to the regulation of basic cell functions via auto-/paracrine mechanisms described above (proliferation, differentiation, secretion of water, ions and mucus, cytoskeleton organization). Acetylcholine also modulates immune functions: release of cytokines, proliferation, cell activation and inhibition. Regarding to the cholinesterases, red blood cells are the blood elements heaviest packed with AChE, whereas BChE is uniformly spread in the liver, lung, smooth muscle and into the bloodstream [3–4]. In this scenario, this cholinergic pitfall comes up as an unapparent source of crucial cellular effects that ACh itself carries out (see Table 1). For decades, a substantial increase of ACh tissue content in chronic inflammatory diseases has been reported, along with increased clonal expansion of the immune system. Beyond the well-known concept of the “inflammatory reflex” [5–6], which reports a reduction of acute inflammatory states after vagus-stimulation, the (non-neural) inflammatory role for ACh is not well understood. In the airway, for instance, the great majority of cells express the components of NNCS and it is documented that a substantial increase on ACh levels triggers the release of proinflammatory effectors [7]. Finally, detailed analysis of the expression and function of non-neuronal acetylcholine may help to gain more knowledge of the pathogenesis of chronic inflammatory pathology of mucosal and skin tissue. The NNCS may be involved in the pathogenesis of chronic inflammatory mucosal diseases, including allergy-related pathology [7]. Up-regulated epithelial acetylcholine may cause an impairment of the barrier and immune functions. It will be a major goal for further research to identify the physiopathological conditions in which the system is up- or down-regulated. Additionally, innovative compounds, targeting the expression and function of the NNCS by topical application (for
instance in eye, skin, airways, alimentary tract), should be developed.

All these qualities together may be underlying the so-called "trophic property" of ACh.

**Non-Neuronal Cholinergic System on Human Erythrocytes**

There are much ongoing studies about the cholinergic effects on erythrocytes. A similar mechanism to what happens in vascular endothelial cells may possibly occur with those cells. Non-neuronal relevance of ACh effects on erythrocytic membranes has been questioned by the presence of the acetylcholinesterase membrane-bound enzyme. This issue came up on the grounds that the proper role of erythrocytic AChE is still vague and object of many studies [8–9]. In reality, erythrocytes are the peripheral blood elements with higher levels of this enzyme spanning the membranes, hence regarded as a marker for their integrity. Despite its well-known function in the neuromuscular junctions, the real role(s) of the erythrocyte-related AChE is still to be expounded [9].

Erythrocytes, together with plasma cholinesterase (BChE), are very effective humoral principles to eliminate non-neuronal acetylcholine escaping into the bloodstream. In addition, the specific cholinesterase shows the utmost substrate turnover rate of all enzymes characterized to date in biological systems. This high activity limits, in fact, the action of acetylcholine within one cell's microenvironment, preventing acetylcholine from working as a hormone for actions remote from its place of synthesis. In parallel, the ACh muscarinic receptors were characterized in erythrocytes as type M1 [10].

One first effect of non-neuronal acetylcholine regards to its influence on the hemorrhological and oxygen-carrying properties of human erythrocytes (see Fig. 2) [11]. Red cell rheology in particular has been focus of interest in the course of time, given the fact that the presence or prognosis of cardiovascular diseases are linked to an increased and/or abnormality of one or more blood properties. According to prior studies from our Vascular Biopathology Unit, ACh induces changes in erythrocyte aggregation and deformability, plus lipid membrane fluidity. Aggregation and deformability are two close-associated properties on which blood viscosity is largely dependent. Under normal blood flow, red cells most aggregate in post-capillary venules, where there is a shear stress decrease; on the other hand, the ability to deform is a property of red cells related to its rigidity, essential for their passage through narrow capillaries with lower diameters than themselves. An in vitro study from our research team revealed ACh decreases erythrocyte aggregation and increases deformability (at lower shear stress), when present in aliquots blood samples from healthy donors. Moreover, ACh augments lipid fluidity, which is an index of order and rate of phospholipids movement in the bilayer [12–13]. The changes in hemorrhologic properties of the erythrocyte have physiological relevance, as they trigger changes in blood viscosity, modulate tissue oxygenation and the distribution of blood in the diverse vascular territories.

Additionally, in the presence of ACh a significant decrease on plasma pH, K⁺ and Na⁺ concentrations, plus an increase on Ca²⁺ concentration as well as on P50 values was detected. Further evidence discloses that dependent on NO levels there are different erythrocyte structural and functional properties. Increasing NO concentrations prompt lipid membrane fluidity and P50 reduction, unlike deformability and methemoglobin concentration which undergo an enhance. In the presence of spermine NONOate, nitric oxide donor, the same results are stated, along with an increase of plasma pH and a decrease of Na⁺ and Ca²⁺ concentrations [12].

Another chapter is the erythrocytes ability to release their NO stockpile, previously bound to hemoglobin which is considered a chariot for NO bioactivity. A parallel study of what occurs in the endothelium illustrated significant alterations in the metabolism of erythrocytic NO and its oxidative metabolites, nitrates and nitrates (NO₃⁻), on ACh-treated erythrocytes [14]. This issue will be dissected further in this article.

Our research group comprises particular hypotheses to explain the supracited ideas, according to ongoing submitted works (see Fig. 3). The action of non-neuronal ACh on erythrocytes could occur by: (i) binding to the AChE with activation of an unidentified protein G, which would modulate the band 3 protein activity; this interaction could be the basis of NO translocation among nitrosylated molecules and phosphorylated/dephosphorylated band 3 protein, respectively by protein tyrosine-kinases and phosophotyrosine-phosphatases; (ii) binding to its muscarinic receptors activating the protein G-dependent phospholipase C enzyme, and leading to protein kinase C activation with cytoplasmatic calcium enhance: (iii) inner "cross-talk" processes upon cAMP and/or cGMP formation by adenylyl cyclase and/or guanylate cyclase activation, correspondingly [15].

Recent data illustrates that the level of phosphorylated/dephosphorylated tyrosines of band 3 domains is able to manipulate ACh's influence on human erythrocytes, mainly regarding the mobilization and metabolism of intraglobular nitric oxide. The ACh-AChE active complex is related with phosphorylated band 3 protein.
ments/procedures, in order to improve the committed microcirculation in cardiovascular patients; (iii) the suggestion of new therapeutic targets for circulation disease, similar of what happens with vascular dementia and Alzheimer’s disease in which, for now, anti-cholinergics are the therapeutic of election.

All things considered, these observations will open a new avenue of research of the old molecule acetylcholine and its biological functions in nature.

**Acetylcholine and Nitric Oxide Bioactivity**

A variety of pathophysiological processes in microcirculation disease is featured by explicit alterations in the nitric oxide (NO) intracellular and plasma metabolism. NO either acts as an important endothelium mediator or upholds a targeted delivery upon blood cells, being capable of controlling the blood flow [16]. Characteristically, erythrocytes are known to play a key role in a wide range of hemorheology processes. After entering red blood cells by simple random diffusion, NO may be either stored or recur to the bloodstream as an active S-nitrosothiol molecule. Particularly, it interacts with the erythrocyte membrane molecules along with hemoglobin, forming S-nitroso-hemoglobin (SNO-Hb), wherein its major intravascular stores are bound. The main biologic metabolites of the NO metabolism are represented by NO₂ and include both nitrates and nitrites [17].

The machinery of release and chemical form of NO-bound compounds in the erythrocyte cytoplasm is poorly settled so far, although it is purpose of several ongoing studies. Given that red cells work as NO scavengers, it is well known to allow an important NO-mediated blood flow regulation performed by responses to changing oxygen levels [18–19]. The aforementioned principle should result in capture of NO in highly oxygenated tissues and release in relatively hypoxic ones. In fact, in high oxygen saturation vessels hemoglobin remains in the R-structure and NO is foraged to Fe³⁺ and, afterwards, to Cys β-93; unlike, low oxygen saturation blood vessels prompt T-structure to allow SNO-Hb binding to band 3 protein and, thereafter, to form SNO-band 3.

With regard to the vasodilating action of acetylcholine, hitherto addressed to the vascular endothelium, it is well established that ACh stimulates its nitric oxide synthesis. Subsequently, there is an increase in the levels of the relaxing factor, a guanylate cyclase stimulator, from its natural substrate L-arginine. This effect is mediated by the interaction of ACh with M1 and M3 muscarinic receptors [20–21]. With this in mind, we formerly proposed a similar mechanism inside the red blood cells. Regarding to the participation of other erythrocyte biomolecules, we previously anticipated a hypothesis involving band 3 protein in order to explain the signal transduction mechanism that could be associated with nitrite and nitrate production [15]. Membrane band 3 is a multifunctional protein containing four tyrosine residues which phosphorylation level modulate the physiological status of erythrocytes by regulating glycolysis, cell shape and membrane transport. Regardless of the higher enrichment of shed vesicles in AChE when compared to band 3 molecules, we hypothesized that changes in band 3 conformation could occur when ACh binds to AChE. Preliminary data are consistent with the idea that the enzyme-substrate complex is

![Fig. 3 Possible erythrocytic mechanisms to explain acetylcholine-dependent modulation: (i) via cyclic nucleotides and NO production and metabolism; (ii) via haemoglobin-oxygen affinity alteration (PSO values); (iii) via modulation of the band 3 phospho-tyrosine level status.](image-url)
Acetylcholine and Vascular Disease

ACH’s vasomotor response is NO-dependent and the loss of its biological activity and biosynthesis is one of the mechanisms responsible for vascular disorders. Atherosclerosis, hypertension, diabetes, reperfusion injury and vasculopathy in general, as well as angioplasty, bypass surgery and transplantation are examples of diseases/procedures in which NO deficiency induces endothelium dysfunction. There is increasing evidence of associations between hemorheological properties and hypertension-changed parameters [27–28]. In a recent experiment, we stimulated human erythrocytes obtained from subjects diagnosed with hypercholesterolemia, renal transplantation and hypertension, with acetylcholine in vitro (10 µM) [29]. We measured the NO levels, hemoglobin and hematocrit values, erythrocyte aggregation, erythrocyte deformability, plasma viscosity and fibrinogen concentration, and afterwards compared the outcome with the achieved on blood samples from healthy donors. In each of these dysfunctions, one verified increased NO production after ACh stimulation, albeit statistical significance was only seen in the hypercholesterolemic group. According to the literature, recent studies are suggesting oxidized LDL forms specifically impair NO-dependent arterial relaxation through different mechanisms [30].

Concerning our results [29] (see Table 2), patients with hypercholesterolemia showed significantly enhanced erythrocyte aggregation, plasma viscosity and fibrinogen concentration, in conjunction with impaired erythrocyte deformability. Previous studies showed the enrichment of cholesterol/phospholipids to prompt elevated plasma viscosity and reduced deformation capacity [31]. We can predict that physiological repercussions of either higher or lower aggregability are attenuated with changes on NO production, or vice versa. Erythrocytes can produce high NO levels even when erythrocyte deformability is decreased, and low NO concentrations when erythrocyte aggregation is increased. Kidney transplant recipients also revealed augmented erythrocyte aggregation and plasma viscosity values, and impaired erythrocyte deformability. Both plasma viscosity and fibrinogen levels are significantly increased in vascular disorders.

The changes on hemorheological parameters and on NO concentration may play an important role in the development of the hypertensive state, that can propose a potential target for vaso-dilating therapy at the microcirculatory level [32]. In agreement,

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<th>Hypercholesterolemia</th>
<th>Renal Transplantation</th>
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<td>Aggregation (nd)</td>
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<td>Plasma viscosity (mPa.s)</td>
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<td>Fibrinogen (mg/dL)</td>
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we may suppose that the erythrocyte aggregation of hypertension subjects could be related with changes on the NO stockpile. In ill patients, there was higher tendency for erythrocytes to aggregate and lower ability to produce NO after ACh stimulation. The power of erythrocyte rheological behaviour might be compensated by NO production in the presence of physiological acetylcholine. though. Beyond its different physiological functions, the hypothesis of a transmembrane signalling mechanism explaining these changes on NO levels simultaneously with perturbations in aggregation/deformability forces is still uncertain.

We might hypothesize that cholinergic/anticholinergic drugs could be used as co-adjuvants in the monitoring of chronic vascular disease.

**Summary**

To review, the non-neuronal cholinergic system, widely expressed in human cells independent of a nervous function, represents a local regulatory system contributing to cell and organ homeostasis.

Acetylcholine represents an extremely old molecule on the evolutionary time scale (about three billion years), is widely expressed in biological systems, can be demonstrated in more or less every human cell and is involved in the regulation of vital cell functions. The ubiquitous expression indicates ACh might probably act as a global player in nature. These findings should be considered, when the physiological/therapeutic role of acetylcholine is discussed.

Based on the ubiquitous expression of non-neuronal acetylcholine and its role in maintaining cellular phenotype, an impaired expression or function of the non-neuronal cholinergic system should result in impaired cell/organ homeostasis. It is an essential task to clarify the pathophysiological role of the non-neuronal cholinergic system in more detail to develop new drugs which can target the synthesis, release, inactivation and cellular activity of non-neuronal acetylcholine.

**Acknowledgements**

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Abbreviations

AChE acetylcholinesterase  
Ach acetylcholine  
BChE butryrycholinesterase  
ChAT choline-acetyltransferase  
COHb carboxyhemoglobin  
DTT dithiothreitol  
Hb haemoglobin  
MetHb methemoglobin  
NO nitric oxide  
NOx nitric oxide metabolites  
NO3 nitrites  
NO2 nitrates  
PTK protein tyrosine kinase  
PTP protein tyrosine phosphatase  
VLM velacrine maleate

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The Use of Panax Ginseng in Sports

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Abstract

The efficacy of Panax ginseng as an ergogenic aid in endurance, seen as maximal oxygen uptake (V0₂max), and lower body explosive power was studied. Maximal oxygen uptake (ml·kg⁻¹·min⁻¹) and explosive power (W.), were monitored by using the multistage 20m shuttle-run test (MSRT) and the Sargent jump test (SJ) respectively. The participants of this single-blind, cross-over study consisted of thirty-four male volunteers from a local 3rd Division amateur soccer team. They were divided pseudo-randomly into three groups (A, B and C). Group A (n=10) was supplemented with Panax ginseng, whilst Group B (n=10) was supplemented with a placebo, both for 6 weeks. Following a two week wash-out period supplementation trends were crossed-over for another 6 weeks. Group C (n=14) acted as the control group. The One-way ANOVA test was used for group data comparability, and the Paired student’s t-test was used to determine the significance of Panax ginseng supplementation. Since P-values of V0₂max (P=0.981) and explosive power (P=0.783) were > 0.05, the data of ginseng supplemented, placebo supplemented and control groups could be compared in both sporting parameters. Improvement in V0₂max on Panax ginseng supplementation was visible and statistically significant (P=0.002 < 0.05). Explosive power improvement on Panax ginseng supplementation was negligible and statistically insignificant (P=0.845 > 0.05). Results of this study have shown that whilst ginseng supplementation did not support any ergogenic effect on lower body explosive power, it influenced V0₂max positively and significantly. Additional research, taking into account fundamental design considerations, needs to be performed for better establishing Panax ginseng’s pharmacological properties and extent of its ergogenic properties (Bahrke MS and Morgan WP, 2000).

Keywords
Panax ginseng, maximal oxygen uptake, multistage 20m shuttle-run test, Explosive power, Sargent jump test, cross-over, control.

Introduction

Athletes at all levels explore ergogenic aids (Eichner, 1997). An ergogenic drug is termed as the administration of any substance, foreign to the body or any physiological substance taken in an abnormal quantity or taken by an abnormal route of entry into the body with the sole intention of increasing, in an artificial manner, the athletes’ performance in competition (Ahrendt DM, 2001). According to Williams, 1984, there are five different classes of ergogenic aids. These are pharmacological, mechanical, psychological, physiological and nutritional.

Ergogenic drug use is as ancient as sport itself. Although pharmacological agents were the principal ergogenic aids utilized particularly in the recent past, their abuse (such as with anabolic androgenic steroids and stimulants) and subsequent increase in mortality of athletes was followed with drug testing to unfoil doping (Caprino L, et al. 2005). As a result athletes have been searching for ergogenic aids with the least side-effects and that cannot be detected during testing. Nutritional ergogenic aids are definitely not overlooked. Here the knowledge and role of the pharmacist definitely comes into play (Ambrose PJ, 2005) Nutritional ergogenic aids may be theorised to improve performance in athletics in a variety of ways, primarily by enhancing energy efficiency, energy control or energy production (Williams, 1995).

Herbal extracts have been used throughout history to enhance physical performance, but scientific scrutiny with controlled clinical trials has only recently been used to study such effects (Bucci, 2000). Herbal extracts currently used to enhance physical performance include, *Panax ginseng*, *Panax quinquefolium*, *Eleutherococcus stenocarpus*, *Tribulus terrestris*, Bulgarian tribulus and saw palmetto berries. Of these, *Panax ginseng* was considered for the clinical trials carried out in this study. The main active constituents of the *Panax* species are considered to be triterpenoid glycosides or saponins, termed ginsenosides by Japanese researchers and panaxosides by Russian workers.

According to Kiefert D. and Pantuso T (2003), a number of research studies indicate that extracts of *Panax ginseng* affect the hypothalamic—pituitary—adrenal axis and the immune system, which could account for many of its documented effects.

The following pharmacological properties are taken into consideration for their purported ergogenic properties. Results from animal studies indicate that *Panax ginseng* enhances exercise endurance by altering full homeostasis, by increasing free fatty acid utilisation in preference over glucose for cellular energy demands. Thus *Panax ginseng* appears to exert a stimulating effect on substrate metabolism by significantly altering lipid and carbohydrate mobilisation and utilisation. Since substrate metabolism is crucial to exercise performance, *Panax ginseng* may be helpful as an ergogenic aid in this way. They also found that a preparation devoid of ginsenosides Rg₁ and Rb₂, failed to enhance, whereas injection of either Rg₁ or Rb₁ enhanced aerobic exercise performance. This further confirms that ginsenosides are the major active constituents (Wang and Lee, 1998). A plausible pharmacological pathway encountered regarding its anti-fatigue and tonic properties is that *Panax ginseng* due to increased occupancy of positive and negative feedback stress hormone receptors and by their natural ligands due to inhibition of specific enzymes which function to limit receptor-occupancy, increases energy by redistributing the body’s energy reserves (Gaffney BT et al., 2001).

No studies were found to indicate any ergogenic effect of *Panax ginseng* with regards lower body explosive power.
Given the currently sparsely documented and conflicting experimental scientific evidence regarding potential ergogenic effects of Panax ginseng in humans and considering the widespread use of this herbal plant root extract, the following analysis on the efficacy of Panax ginseng as an ergogenic aid in sports performance was carried out. This was achieved by verifying the efficacy of Panax ginseng supplementation in endurance, expressed as maximal oxygen uptake or VO$_{2\max}$ (ml·kg$^{-1}$·min$^{-1}$), and in explosive power, expressed as watts (W). All experimental procedures were reviewed and acknowledged by the Research ethics committee of the University of Malta.

Methodology

Participants
All the participants were members of the same 3rd Division football amateur team. Their height, weight and both the systolic and diastolic blood pressures (see Table 1) were examined by the same fully qualified nurse that supervised their filling in of a participant medical questionnaire. The participants were also asked to avoid taking any medications and/or performance-altering drugs and/or nutritional supplements, during and 6 weeks before the study period, and to avoid changes in level of physical activity, that is to keep attending their daily training sessions regularly. The investigations were initiated three weeks into the pre-season conditioning training period. Although the training sessions during the experimental period were not standardized, the participants were members of the same team and as a result all participants performed the same training programs.

Panax ginseng and Placebo
Each Panax ginseng transparent capsule contained pharmaceutical-grade beige powder providing 50mg ginsenosides which is equivalent to 2000 mg Panax ginseng dried root. One must mention that the capsules contained no added sugar, starch, flavour or yeast.

As no placebo capsules could be purchased it was decided that they were to be prepared. Each transparent, empty capsule (0.11 ± 0.01 g) was then filled with 0.41 ± 0.01 g of Cerelac® wheat and milk powder. The filling procedure was carried out in a sterile chamber at the Department of Pharmacy, University of Malta. Both the Panax ginseng powder and the placebo powder were beige in colour, had similar texture and appearance.

Investigations
The participants were assigned pseudo-randomly to either Group A (n=10), Group B (n=10) or Group C (n=15). A single-blind, cross-over research design was pursued to administer the Panax ginseng and placebo supplements. The investigations were divided into period 1 and period 2 with a two week wash-out period in between.

During period 1 Group A was supplemented with the Panax ginseng capsules (taken once daily) for forty-two days. Group B was supplemented with the placebo capsules (taken once daily) for forty-two days and Group C was kept as the control group, and took no supplement whatsoever during these forty-two days. A two-week wash-out period followed so that the same participants could be used in the cross-over without the influence of previous supplements.

During period 2, this time Group A was supplemented with the placebo capsules for forty-two days and Group B was supplemented with the Panax ginseng capsules for forty-two days. Group C was only needed to be investigated once and thus was not included in period 2 investigations.

Both the multistage 20-metres shuttle-run test (MSRT) and the Sargent jump test (SJT) were carried out for both pre-supplementation and post-supplementation testing of both period 1 and period 2. The MSRT was employed to help determine the participants' maximum oxygen uptake (VO$_{2\max}$). It was used in the pre-supplementation and post-supplementation investigations of both period 1 and period 2. The multistage 20-metres shuttle-run test (Leger LA et al., 1998) involved running continuously between two points that were twenty metres apart. These 'shuttle' runs were done in time to pre-recorded 'bleep' sounds on a pre-recorded CD. The participants stopped running either when they could no longer keep up with the speed set by the CD or when they failed to reach the end of the shuttle before the 'bleep' for three consecutive shuttles. The following regression equation (St. Clair Gibson A et al., 1998) was used:

\[ Y = 6.0 \times (X_1) - 24.4 \]

Where \(X_1\) = the maximal shuttle run speed (Km h$^{-1}$) and \(Y\) = the predicted VO$_{2\max}$ (mg·min$^{-1}$·kg$^{-1}$).

On the other hand the Sargent Jump test was used to measure explosive power of the participants. The athletes performed the

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Sargent jump test in the following way. Each athlete was asked to stand sideways on to the three meter wall mentioned. The hand on the side close to the wall was lifted above the head stretched as much as possible with the feet kept flat on the ground. The point of the fingertips was recorded onto a purposely designed recording sheet. In this way each athlete’s reach was recorded. From the same sideways standing position, each athlete made a quick flexion of the legs and using both arms to assist in projecting the body upwards jumped as high as possible to place the Velcro cylinder (which was kept in the hand closest to the wall) on the board. In this way the point of reference from which the sargent jump was to be measured was established.

The athletes first performed a number of test jumps to familiarize themselves with the jump until they felt comfortable with their jump. Following this they performed two jumps each, with a rest of thirty seconds in between the two jumps. Only one participant at a time was tested.

The average jump height was obtained by using the following equation, where $H_r$=reach height and $H_{sp}$=sargent jump height.

\[
\text{Average Jump height (cm)} = \frac{(H_r - H_{sp}) + (H_r - H_{sp})}{2}
\]

The following calculation (Sayers et al., 1999) was used to convert jump height into a power score.

\[
\text{Explosive Power (W)} = [60.7 \times S \text{ height (cm)}] + [45.3 \times \text{body mass (kg)}] - 2055
\]

**Statistical Analysis**

Standard statistical techniques were used to calculate means, standard deviations, averages, standard error of means, and linear correlation coefficients using Microsoft Excel™ operating in a Windows environment. A one-way analysis of variance (ANOVA) was carried out on the pre-supplementation results to make sure and subsequently show that the control group when compared to test groups A and B are similar in their values and results. This will impart greater reliability to the investigation. Otherwise, differences were examined using a paired student’s t-test. The t-test is paired due to the use of the cross-over design, that is both athletes in Group A and Group B were tested under the influence of *Panax ginseng* capsules and placebo capsules. The level of significance used to reject the null hypothesis was set at $p < 0.05$ for all comparisons. Unless otherwise stated, values are presented as mean ± SEM.

Analysis was performed by using the Analyse-it statistical package (Analyse-it, v1.61).

**Results**

Six athletes out of a total of forty failed to participate throughout the whole study. Three of the athletes stopped attending training sessions and as a result were excluded. On the other hand, the other three athletes chose to withdraw from as they sustained injuries either whilst training or playing in friendly matches. As a result, their initial contributions to the study were omitted.
of Panax ginseng versus Placebo, Panax ginseng versus Control, and Placebo versus Control. These results supported the previously mentioned statistical significance, suggesting that Panax ginseng effected positively and significantly maximal oxygen uptake of the supplemented group when compared to the other groups.

Sargent Jump Test Results
In Figures 4 and 5, the values are categorised according to whether a jump value is poor, below average, average or above average for both pre-supplementation and post-supplementation tests.

There was no difference between the Panax ginseng supplemented, placebo supplemented and control groups in sargent jump performance, as measured by the jump distance achieved in any one of the two trial jumps, prior to the supplementation protocol.

Following six weeks of supplementation and training, jump distance values increased greatly in both the Panax ginseng group and the placebo groups. However this was not the case with the control group which decreased in performance (see Fig 6).

A student’s t-test was carried out at a 5% level of significance to analyse Pre- to Post- differences for the 3 groups. A statistically significant difference was obtained for Panax ginseng and placebo supplemented groups, but not for the control group.

The student’s t-test was again used to analyse the % changes and absolute changes of Panax ginseng versus placebo, Panax ginseng versus control and placebo versus control. These results did not substantiate the statistical significance mentioned previously. Thus although there was a statistically significant difference between the post-test results and the pre-test results for both participants of Panax ginseng and placebo there was no statistically significant differences in the magnitude of the improvement between the groups.

Discussion
Accurate and reliable measurement of physical activity and physical fitness is critical in conducting research designed to evaluate how they influence dietary requirements and whether supplements can enhance physical performance.

As a result the components of physical fitness to be tested and their relation to physical performance were established before carrying out the investigations. This is extremely important in choosing the most appropriate measuring technique and overcoming problems or limitations that might occur (Haskell and Kiernan, 2000).

MSRT is a maximal and progressive test that allows trainers and coaches to predict maximal oxygen uptake (VO2max) from sub-maximal or maximal incremental exercise. The type of event for which the participant is trained may influence the outcome of
the test and the prediction of VO\textsubscript{2}max. It must be said that a slight anaerobic element may have a role to play in MSRT scores. For instance it was particularly noticeable, especially at higher levels, that turning technique was important and those who turned most economically fared best. Also, after turning at the end of each shuttle the participant must accelerate to obtain the desired speed. Furthermore during the latter stages of the MSRT, the anaerobic metabolism component will be increased as the individuals' aerobic system becomes fully taxed. Thus an individual with a low anaerobic power may not preform as good as the MSRT relative to his aerobic power. Having said that, this test was employed in this study (and not others such as the cooper's test, CONCONI test) since according to Grant S et al., (1995) MSRT may be more relevant to game players where turning and the anaerobic component are a feature of the game, and the participants all played football.

In fact St Clair Gibson et al. (1998) compared the use of this test in long distance runners (continuous high-intensity exercise) and squash players (intermittent high-intensity exercise). There was a greater under prediction of VO\textsubscript{2}max in runners than in squash players.

Maximal oxygen uptake in this study, as in many other studies, was measured indirectly. In other words the level achieved during the multistage 20m shuttle-run test, was utilised to calculate the maximal oxygen uptake. Engels Hj et al., (1996) pointed out that as oxygen uptake is an important criterion variable it needs to be measured directly rather than estimated. Having said this, one must say that the testing method and the formula implemented to assess maximal oxygen uptake in this study are scientifically tested, found to be reasonably accurate and as such are recommended for predicting VO\textsubscript{2}max (Leger LA. et al. 1988).

No studies addressing the use of Panax ginseng with respect to explosive power have been encountered. A possible reason being that of its proposed mechanism of action, which does not promote an ergogenic effect in such a sporting parameter. However it was interesting to note what results might be obtained with such a parameter on being supplemented with Panax ginseng.

According to Tumility (1993) height attained in a sargent jump is a reliable and valid measure of explosive power. There are a variety of jump tests used to determine explosive power (such as the counter movement jump and vertical squat jump). Also, Shetty (2002) mentioned that using a conventional 'jump and reach' such as the squat jump test, employed in this investigation, one can accurately predict explosive power.

It is important to note that the use of a force platform is considered as the standard measurement of explosive jump power. Having said this, this testing technique is prohibitively expensive and as a result the sargent jump test has become the most widely used method by which explosive athletic performance is assessed since it is convenient, inexpensive and has reasonable accuracy (Sayers et al., 1999).

The results of this study support an ergogenic effect on maximal oxygen uptake (VO\textsubscript{2}max), but not on explosive power following a 6-week supplementation period with 310mg Panax ginseng root powder and 70mg Panax ginseng root extract in healthy male football players with moderate exercise capacities.

The design of this study was as much as possible based on specific research reports dealing with Panax ginseng's ergogenic potential in humans that were recently performed. The effects of Panax ginseng on performance enhancement have been reported for many years, however the published research and evidence documenting the effects of Panax ginseng on performance in humans has been characterised by numerous methodological problems. Also, human experimental research evidence, to support these claims, is limited and conflicting (Bucci, 2000). The latter problem can be easily noted from some interesting studies carried out to verify the use of Panax ginseng as an ergogenic aid (see Tables 2 and 3).

With regards to the this study, to begin with, whilst a number of studies observed non-significant findings in shorter term supplementation studies (1 to 4 weeks) other studies reported an increased work performance following 6 to 10 weeks of Panax ginseng supplementation. As a result it was made sure that the participants in this study were supplemented for a minimum of 6 weeks. Although it is commonplace for studies to note the nature of the participants (e.g. health status, height, weight, age, gender) and the criteria for inclusion, according to Bahreke and Morgan (2000), a large part of the work in this area does not possess such description. It was thus made sure that such data was not overlooked when carrying out these investigations. Also, the participants were clearly explained to follow the dosage regimen given. This was based on instructions presented by the information leaflet regarding the Panax ginseng containing product used and confirmed with all the studies in the area.

<table>
<thead>
<tr>
<th>Author</th>
<th>Participants</th>
<th>N</th>
<th>Dose (mg)</th>
<th>Duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Von Ardennen (1987)</td>
<td>Not specified (42 to 65 yrs)</td>
<td>63</td>
<td>200</td>
<td>4 wks</td>
<td>Change in blood within 2 hrs</td>
</tr>
<tr>
<td>McNaughton (1988)</td>
<td>Marathon runners</td>
<td>30</td>
<td>1000</td>
<td>6 wks</td>
<td>↑ VO\textsubscript{2}max, ↑ HR recovery</td>
</tr>
<tr>
<td>Pieralisi (1991)</td>
<td>Male sports teachers (21 to 45 yrs)</td>
<td>50</td>
<td>200</td>
<td>6 wks</td>
<td>↑ VO\textsubscript{2}max, V\textsubscript{V}, V\textsubscript{CO\textsubscript{2}} at submaximal levels, only in participants with initial VO\textsubscript{2}peak &lt; 60 mL kg\textsuperscript{-1} min\textsuperscript{-1}</td>
</tr>
</tbody>
</table>

Table 2 Panax ginseng supplementation studies supporting an ergogenic effect
Table 3 Panax ginseng supplementation studies not supporting an ergogenic effect

<table>
<thead>
<tr>
<th>Author</th>
<th>Participants</th>
<th>N</th>
<th>Dose</th>
<th>Duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Engels et al., (1999)</td>
<td>Healthy adult females</td>
<td>19</td>
<td>200mg</td>
<td>8 wks</td>
<td>No significant difference in max. work performance, resting, exercise, recovery O₂, RER, VO₂, HR, blood lactate level</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>G115 4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allen et al., (1998)</td>
<td>Healthy moderately fit young athletes</td>
<td>28</td>
<td>200mg 7%</td>
<td>3 wks</td>
<td>No significant difference in VO₂ exercise time, workload, lactate, hematocrit levels, HR, RPE</td>
</tr>
<tr>
<td></td>
<td>Male (20) and female (8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kolokouri et al., (1999)</td>
<td>Healthy adult females</td>
<td>24</td>
<td>400mg 4%</td>
<td>8 wks</td>
<td>No significant difference in short duration, supramaximal work</td>
</tr>
</tbody>
</table>

However, a few methodological deficiencies arose from this study that contributed negatively. Although all athletes that participated in this study declared they took all supplements, their compliance was not monitored, and as a result this cannot be verified. Another drawback was that the nutritional intake of the participants was not monitored, although the athletes were instructed to keep on a healthy diet, once again this could not be confirmed.

The purity of the preparation used was not analysed before the trials were carried out. This is especially important due to recent allegations on possible irregularities regarding the purity of nutritional supplements available on the market (Oelker L., 2005).

Although the athletes were assigned pseudo-randomly, that is affiliating participants to one of three groups—A, B and C—and evaluating participants at baseline level, uniform distribution with regards age, body weight and height was not carried out. This could have caused discrepancies in the results obtained.

Although the participants attended training regularly, missed training sessions could be a source of variation in the results achieved. In addition to this, slight injuries during the supplementation period caused the affected participants to follow a different training regime until the injury healed.

It is important to mention that although both sporting parameters were measured with scientifically accepted methods (reasonably accurate) the most direct measuring equipment was not employed. Since the best and most direct measuring methods and equipment were extremely expensive at the time the study was carried out.

Having the study performed in a double-blind manner would have increased the reliability of results as the influences of the evaluator would have been eliminated also. The placebos were prepared by the investigator himself who also acted as the supplement distributor for those supplemented with placebo and Panax ginseng. None of the participants complained of any unwanted effects following the ingestion of 310mg Panax ginseng root powder and 70mg Panax ginseng root extract for 6 weeks.

In general studies with Panax ginseng extracts are quite limited in quality due to a variety of reasons, namely:

(i) Standardisation of Panax ginseng Extract Being Tested
Extracts from the same root vary in ginsenoside concentrations and content due to the growing environment, age of roots and extraction methods. Moreover, Walker (1999) reported that many of the Panax ginseng preparations found on the market often do not contain the ingredients indicated on the label.

A good solution for this is to determine the purity and ginsenoside content of such preparations prior to carrying out investigations in future studies.

(ii) Confirming User Compliance
Bahk and Morgan (2000), suggest that this could be countered by observing the user as he/she consumes the product, and/or assay of body fluids (e.g. urine, plasma) in order to confirm the level of compliance.

(iii) Employing the Placebo in the Correct Manner and Adequate Documentation as Regards the Way it was implemented
Again Bahk and Morgan (2000), suggest that placebos and Panax ginseng clinical trials be carried out in a double-blind context in order to control for both the Hawthorne effect and Halo effect.

(iv) Supplementation Strategies
The dose of a previously specified ginsenoside concentration should be established per day, following scientifically based supplementation strategies of Panax ginseng. The duration of supplementation should also be based on scientifically based studies. Preferably prolonged supplementation tests should be implemented so as to verify better chronic use of this herbal extract, both regarding its efficacy and its safety.

(v) Large-scale Trials may be More Reliable
The more the sample of participants resembles the population and the larger the sample is, the more reliable the results obtained are.
(vi) Using the Best Equipment
Unfortunately, although a number of scientifically sound equipment is present nowadays more often than not they are extremely expensive. Also the equipment involved should be one that measures the parameter in question directly and not indirectly in order to avoid unwanted discrepancies in the results.

(vii) Standardisation of Training Regime
Although game sports athletes of the same team will be performing the same training sessions, their varying attendances (or missed sessions) may influence the results negatively. As a result providing incentives for those who attend all training sessions or most of them (e.g. at least 80%), might help keeping attending training regularly.

(viii) Mechanism of Action of Panax ginseng
Bucci (2000) states that as herbal supplements with apparent merit are identified further detailed studies on mechanisms would be more efficiently performed. In fact according to Gaffney et al., (2001) the relative lack of coherent models explaining the mechanism of action of Panax ginseng at the molecular level may be part of the reason why these drugs have not yet been examined in large scale controlled clinical trials in humans exposed to severe stressors.

Thus future studies would be directed at a closer look at the pharmacology and pharmacokinetics of this herbal extract.

Conclusion
Presently there is no real solid research support at hand exhibiting Panax ginseng to have ergogenic properties in humans at common dosage levels used, even though a number of studies have supported this.

Thus, as mentioned in previous sections the effect of Panax ginseng as an ergogenic aid still requires further well designed studies that concentrate on testing varying standardised levels of ginsenosides in relation to a variety of age groups, fitness levels and intensities of exercise they perform.

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References


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Gujar Lung—A Disease Mimicking Miliary Tuberculosis

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Abstract

Gujar Lung is a chronic lung disease caused by long term exposure to pinewood smoke inhalation in Gujar community and the people residing at hilly regions of the Indian sub-continent. This is characterized clinically by progressive cough and dyspnea, distinct radiological patterns and pathological features of anthracotic nodules and fibrosis. A typical case with miliary mottling on chest radiograph is presented and the relevant literature reviewed.

Keywords
pine wood smoke, miliary shadows, anthracotic nodules, interstitial lung disease

Introduction

Guajar Lung is an environmental interstitial lung disease caused due to indoor air pollution with pinewood smoke, occurring predominantly in members of the Gujar community—a social and ethnic group residing at high altitude hilly regions of the Indian sub-continent (viz Jammu and Kashmir, Himachal Pradesh, Rajasthan, Pakistan, Pakistan Administered Kashmir and Tibet). These people typically live in very small poorly ventilated dwellings called kothas, made of mud, stones and wood with very low roofs made of wood and crop residues covered with clay. Inside under the same roof, there is a compartment of cattle and where the family members live. In addition there is a Chullah (fixed mud hearth) which is made of clay and stone and is used for cooking there by burning wood, dried cow dung and crop residues for an average of 12 to 16 hours each day. A high oleoresin containing part of the pinewood called Lash is burnt for lighting purpose and is usually kept burning during morning and evening hours creating dense smoky atmosphere in the dwellings, which are very poorly ventilated.

Clinically, the disease is characterized by progressive cough and dyspnea, with onset usually beyond the fourth decade of life; characteristic radiological pattern of miliary mottling, reticulo-nodular shadowing, fibrosis and/or cor pulmonale and presence of anthracotic nodules with carbon-laden macrophages and fibrosis on histopathological examination. The entity was introduced in medical literature in 1991 [1] and since then few more cases have been reported [2,3]. We again describe a case of miliary mottling on chest radiograph misinterpreted as miliary tuberculosis.

Case Report

A 48-years-old male Gujar presented with history of progressive dyspnea and cough with production of blackish sputum. He had no history of fever or loss of weight and there was no other history suggestive of tuberculosis or any other significant illness in his past. He had lived in a kotha since his early childhood. His general physical examination and systemic examination were normal except for the presence of a few crackles in the lower lobes of both lungs on auscultation of chest. X-thorax revealed miliary shadowing in all zones on both sides (Fig.1).

Fig.1 Chest radiograph showing miliary shadows bilaterally, more dense in mid zones peripherally.
Discussion

Chronic exposure to wood smoke and its long term inhalation has been associated with chronic obstruction pulmonary disease, pulmonary arterial hypertension, cor pulmonale, recurrent lower respiratory infections, lung cancer and interstitial lung disease [4–9].

The entity Gujjar Lung was first introduced in 1991 by Dhar and Pathania [1] from Kashmir when they noticed military mottling and reticulonodular pattern in chest radiographs of patients belonging to Gujjar community. These were empirically put on therapeutic trials with antituberculous treatment, but the shadows remained unchanged despite adequate dosage and duration of treatment. Finally lung biopsy was taken which revealed findings of antracotic nodules, carbon laden macrophages and fibrosis. The authors attributed it to the indoor air pollution with smoke from biomass combustion, mainly pinewood. Subsequently Raison et al. [2] form the George Washington University, USA reported HRCT findings in a case of Gujjar lung with similar histopathological features in a Kashmiri baker, who was working in Saudi Arabia. Chest radiographs were taken on the patients as part of routine health checkup prior to his immigration, which showed significant military shadows. History of exposure to pinewood smoke was established. By 2001 Saiyed HN et al. [10] form Ladakh region of Jammu and Kashmir reported military shadowing in chest radiographs of residents of this high altitude region. They described this entity as non occupational pneumoconiosis and attributed to the exposure to free silica from dust storms or domestic wood smoke inhalation, however histopathologic examination was not performed [7].

More recently, Saini et al. [11] from the Postgraduate Institute and the Government Medical College, Chandigarh, India reported similar radiological and histopathological findings in a woman of Himachal Pradesh and described the disorder as wood smoke inhalation associated lung disease. We have been observing and studying such cases for the last 8 years now and the most probable mechanism of lung injury seems to be the long term inhalation of pinewood smoke, as the disease was not found in any of the 4124 individuals who belonged to Gujjar community, but were different in that lived in a different region and were also exposed to intense indoor air pollution with smoke from other biomass fuel (crop residues, dried dung cakes and wood) combustion but were not exposed to pinewood smoke.

Pinewood on combustion yields sulphur dioxide, benzopyrene, carbon monoxide, nitrogen oxides, polycyclic hydrocarbons and low molecular weight aldehydes including acrolein and albeatic acid. These gases individually or along with carbon could be responsible for lung injury and fibrogenic reaction [1, 2, 7, 11]. Coal macules formed in the lungs followings a prolonged exposure to carbonaceous dusts and the resulting fibrosis is postulated to give rise to the characteristic radiological appearance of military and reticulonodular shadows [1, 9, 11].

The entity needs to be differentiated from coal worker's pneumoconiosis which has similar histopathological appearance, but the patient's, ethnic origin, history and exposure and occupation help to differentiate it from the later. Cryptogenic organizing
pneumonia is differentiated by the absence of polypoid granulation tissue within the lumen of bronchioles and alveolar ducts [1, 2]. Gujjar Lung is of paramount importance from treatment point of view because such cases are empirically being subjected to anti-tuberculosis drugs resulting in unnecessary wastage of resources and exposure.

Further studies involving large samples are needed to see the injury patterns, genetic predisposition and the reactions evoked in the lungs. Moreover, as the data suggests for now, prevention involves to change the living standard of this community, so as to prevent exposure to pine wood smoke inhalation. Provision of electricity as the safest and cleanest source of fuel, through appropriate government policy is expected to prevent occurrence of this disorder.

References

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