Series of Publications of I.O.M.S

Islamic Organization
for Medical Sciences
(I.O.M.S.)

Kuwait Foundation for
Advancement of Sciences
(K.F.A.S.)

Bulletin of Islamic Medicine
Vol. 5

Proceeding of
The Fifth International Conference on

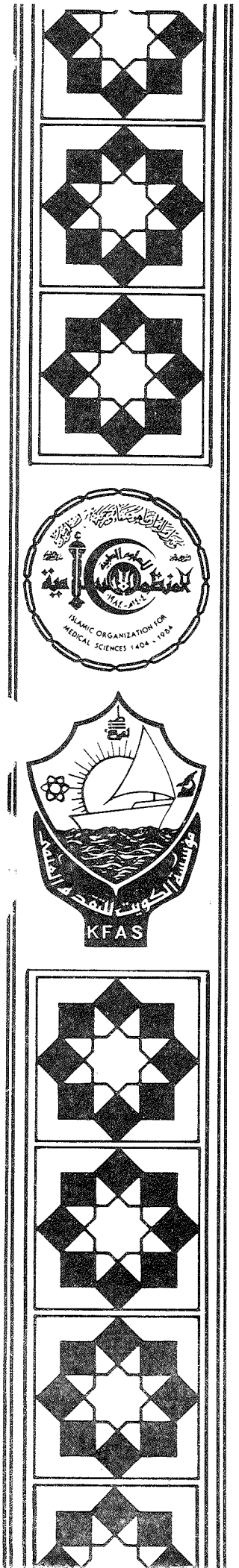
Islamic Medicine

Supervised by
H.E. Dr. Abdul Rahman Abdulla Al-Awadi

The Minister of Planning,
and
President of Islamic Organization
for Medical Sciences

Edited by
Dr. Ali Yousuf Al-Saif
Dr. Ahmed Ragai El-Gindy
Professor Mohammad Sabir

Rabi'l II, 1409/November 1988
State of Kuwait



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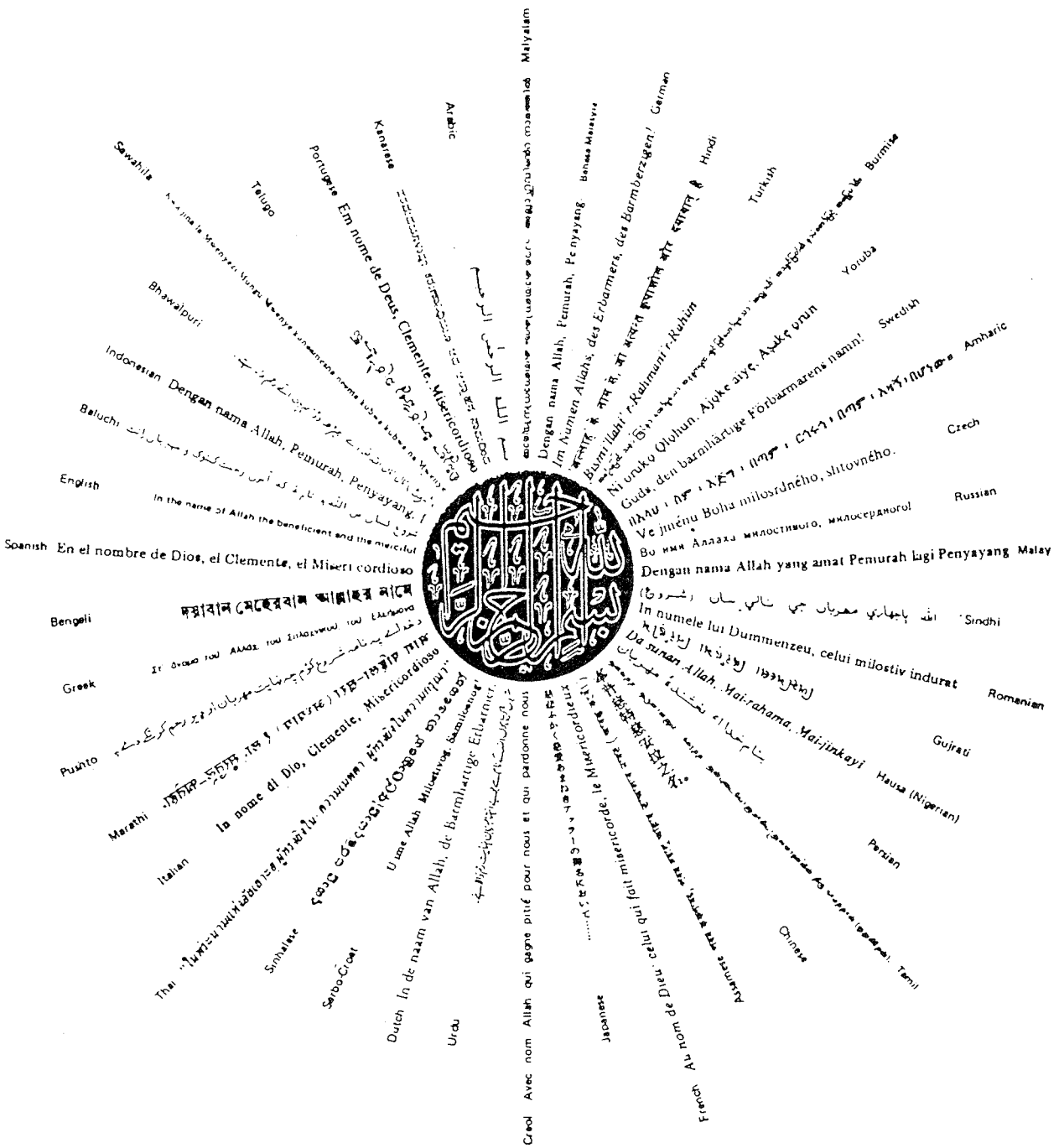
English
In the name of Allah the beneficient and the merciful
Spanish En el nombre de Dios, el Clemente, el Miseri cordioso
Bengali
Greek
Pushto
Marathi
Italian
Thai
Sinhalese
Serbo-Croat
Dutch In de naam van Allah, de Barmhartige Erbarmer.
Urdu
Creol Avec nom Allah qui gagne pitié pour nous et qui pardonne nous
Japanese
French Au nom de Dieu, celui plein miséricorde, le Miséricordieux.
Chinese
Persian
Tamil
Hausa (Nigerian)
Gujrati
Romanian
Malay Dengan nama Allah yang amat Pemurah lagi Penyayang
Sindhi
Russian
Czech
Amharic
Swedish
Yoruba
Burmese
Turkish
Hindi
German
Malyalam
Arabic
Kanarese
Portugese Em nome de Deus, Clemente, Misericordioso
Telugo
Swahili
Bhawalpuri
Indonesian Dengan nama Allah, Pemurah, Penyayang
Baluchi

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IN THE NAME OF GOD MOST GRACIOUS AND MOST COMPASSIONATE

FOREWORD

Dr. Abd al-Rahman Abd Allah al-Awadi
Minister of Planning, and
President of the Islamic Organization for Medical Sciences
KUWAIT

With the guidance of God the Fifth Conference on Islamic Medicine was held in the Arab Republic of Egypt in the period between 10-13 of Rabii al-'Aakher 1409 Hij. corresponding to 20-23 of November, 1988.

While the third conference was held in Turkey, the fourth in Pakistan, but this one is special as it was held in cooperation with al-'Azhar al-Shariif, with the status it holds in the Islamic world and the Egyptian Medical Association, with its standing and size in the Arab and the Islamic world. So most of the papers and the discussions were of very high level in both content and presentation.

These papers have dealt with urgent issues, particularly since these were presented in the Arab Republic of Egypt with its Islamic, Scientific and demographic standing. We dealt with the issue of the programmes presented in our Medical schools from an Islamic perspective with the purpose of attracting attention to the importance of this highly interesting issue and what these programmes should include for our sons, the physicians of the future, in terms of the study of our legacy, so as to help them regain their confidence in themselves as well as make them feel that Islam has an important role to play. So that they can see that when our ancestors staunchly held on to the world, they dominated it and won the hereafter as well, and that Islam is a launching pad for the future. The goal of such a conference is not to confine ourselves within hard and fast traditions, nor is it an attempt to boast of the greatness of Islam, but as a forum for study and assessment.

The second thing that we were keen to include in the programme of medical schools is Medical jurisprudence and professional ethics.

In spite of the fact that Medicine is a universal human legacy that generations inherit from one another, one generation following the other, yet like all other arts it flourishes and withers depending on the cultures surrounding it. In any case, medicine is a humane profession.

Today as secular materialistic trends prevail everywhere, with the many calls of western scientists that science should exist only for scientific purposes, and that science should disassociate itself from wisdom, and the many tendencies which have left their impact on Western societies. Courts are now witnessing many problems involving the mixing of parenthood and womb *(khalt al-'Ansaab wa al-'Arhaam),* everyone stands confounded before these cases, because they have abandoned the divinely revealed legal codes and set about making their own, in their belief that they can do better for themselves. So the truth has now been lost and the ship is about to sink with every one on board.

Whereas Islam, in comparison with all other sects, is distinguished by being the revelation of God Almighty who knows man better than himself, knows all that the self says, is closer to man than his most vital arteries, and has shown him the permitted and the forbidden as well as commanded him to follow his commands and prohibitions, because they were legislated for the welfare of man.

So we were keen that this matter should be included in the programmes of medical schools.

As for the second issue, dealing with the plagues of our age such as narcotics, alcoholic substances, and sexual license and obscenity, the situation is more serious than what is openly revealed in the statistics, as

these do not usually reveal the reality of the situation. Therefore, I call upon all, the governed and the governors to pay attention to this serious problem, in order to preserve our youth who are the pillar of our nation and its future.

These were the most important issues deliberated at the Fifth Conference on Islamic Medicine, in addition to the other topics dealing with applied matters and the issue of medical miracles in the Koran.

The Islamic Organization for Medical Sciences is always trying to deliberate these issues which it believes will have a significant impact on the path of the nation of Islam in general, and particularly those that pertain to medicine, in the hope that it will attract attention to their significance and their importance.

We pray to God that we have given these two issues the importance they both deserve.

We would like to thank everyone for their participation either with their papers or in their interventions, or even by their attendance, as they are all the real asset of the Islamic Organization for Medical Sciences. I pray to Almighty God to guide us to His will.

"al-Salaam Alaykum wa Rahmtu Allah".
Peace and blessings of God be upon all of you.

IN THE NAME OF GOD MOST GRACIOUS AND MOST COMPASSIONATE

EDITORIAL

With God's guidance, the Fifth Conference on Islamic Medicine was held in the Arab Republic of Egypt, with the collaboration of al-'Azhar al-Shariif and the Egyptian Medical Association in the period between 10-13 Rabii al-'Aakhar 1409 Hij., corresponding to 20-30 of November 1988.

The conference this time adopted the separate session format, so the participants were divided into two groups, each group met in separate halls from morning until evening to deliberate the submitted papers, then both groups met together in the evening in one hall, when the rapporteur of each group presented a report on the events in his session, followed by the deliberation of both groups.

This format has its advantages and its shortcomings, on the one hand it gave us the opportunity to present a large number of papers and we had ample time to conduct our deliberations separately in each session. This in itself is one of the things that we have surely missed in previous conferences.

However, the rapporteur's reports were not always of the same format or the same level of proficiency, some were excessively short whereas others were excessively long and detailed, it all really depended on the rapporteur. Moreover, the participants were very interested in the issues under consideration in both session at once, and this caused some difficulty in dividing the participants between the two halls.

Moreover, this conference was different from previous ones in that most of the participants knew Arabic except for one or two scholars, in view of our long experience of simultaneous interpretation and the problems it usually causes because of its imprecision, either because of the speed of delivery, or the speaker improvises and is not committed to his written paper, or the difficulty of the Arabic language in general, or the difficulty of jurisprudence terminology in particular. Therefore, the number of papers written in English was small and we have therefore decided to publish both the Arabic and the English papers in one volume.

Furthermore, some of the participant scholars have not responded to our correspondence concerning the sending of their papers in their final form, so we included instead the abstracts of these papers.

Moreover, not all the papers on medical miracles in the Koran were received, and therefore we have included their abstracts, which were already to hand, in the Arabic Section.

In conclusion, these are the proceedings of the Fifth Conference on Islamic Medicine, and we have done our utmost to produce them in the best form possible, praying to Almighty God to guide us to His will and wishes, for God is the only guide to the straight and narrow path.

"al-Salaam Alaykum wa Rahmatu Allah wa Barkaatih".
Peace and blessings of God be upon all of you.

Dr. Ali Yousuf Al-Seif
Dr. Ahmed Raja'i El-Gindi
Professor Mohammad Sabir

PROGRAMME OF THE FIFTH CONFERENCE ON ISLAMIC MEDICINE & THE SECOND CONFERENCE ON THE MEDICAL MIRACLES IN HOLY QURAN

NOVEMBER 20-23, 1988
CAIRO, EGYPT

FIRST DAY: SUNDAY, NOVEMBER 20, 1988

OPENING CEREMONY: (09.15-11.00)

— Recitation from Holy Quran (09.00-09.10)

— Dr. Ali Yusuf Al-Saif, (09.10-09.25)
Secretary General of I.O.M.S.

— Dr. Abd El Monem Aboul Fatouh (09.25-09.40)
Secretary General of Egyptian Medical Syndicate

— Prof. Dr. Mamdooh Jaber, (09.40-09.55)
President of Egyptian Medical Syndicate

— H.E. Dr. Abdul Rahman A. Al-Awadi (09.55-10.10)
President of Islamic Organization for Medical Sciences (IOMS)

— Sheikh Jaad Al-Haq Ali-Jaad Al-Haq (10.10-10.25)
Imam of Al-Azhar Al-Shareef

— H.E. Dr. M. Ragheb Dowaidar (10.25-10.40)
Minister of Health, Egypt and Representative of H.H. the President of Egypt

— Distribution of the Prizes and Shields of Islamic Organization for Medical Sciences, offered by Kuwait Foundation for Advancement of Sciences, (KFAS) (10.40-11.00)

SECOND DAY: MONDAY, NOVEMBER 21, 1988

FIRST SESSION:

MAIN ROOM

Time (09.00-11.00)

PLENARY LECTURES:

Chairman: Prof. Dr. Ahmed Kamal Abulmagd

Moderator: Prof. Dr. Tawfik Al-Tamimy

Speakers:

1. Prof. Dr. Abdul Aziz Kamel *Youth Between Innocence and Guilt.*	(09.00-09.45)
2. Prof. Dr. Mohey Al-Deen Saber *Heritage and its Relation with the Future Prospects of Moslem World.*	(09.45-10.30)
3. Discussions	(10.30-11.00)
Break	(11.00-11.15)

SECOND SESSION:

FIRST ROOM

Time: (11.15-14.30)

CURRICULUM OF THE FACULTY OF MEDICINE FROM THE ISLAMIC VIEWS

Chairman: Prof. Dr. Khairy Al-Sammrah

Co-Chairman: Prof. Dr. Abdullah Ba-Salama

Moderator: Dr. Fahad Al-Ghanim

Speakers:

(A) HERITAGE

1. Prof. Saeed A.F. Ashour *The Importance of Studying the Islamic Medical Heritage in the Faculty of Medicine*	(11.15-11.30)
2. Prof. Dr. Ibrahim Bin Morad *Islamic Medicine Heritage*	(11.30-11.45)
Prayer	(11.45-12.00)

(B) MEDICAL JURISPRUDENCE

1. Prof. Dr. Khaled Al-Mazkour *The Need of the Faculty of Medicine to the Islamic Jurisprudence.*	(12.00-12.15)
2. Dr. Mohammed Ali Al-Bar *Suggestion of Islamic Medical Programme for the Faculty of Medicine.*	(12.15-12.30)
3. Prof. Salem Nejam Salem *Islamic Medical Curriculum.*	(12.30-12.45)
4. Discussions	(12.45-14.30)
Break and Prayers	(14.30-17.30)

SECOND SESSION:

SECOND ROOM

Time: (11.15-14.30)

DISEASES OF ERA

Chairman: Prof. Dr. Ahmed Khaleefah

Co-Chairman: Prof. Dr. Adel El-Sobky

Moderator: Dr. Abdussattar Abu Ghudah

Speakers:

1. Dr. Ahmed El-Kadi (11.15-11.30)
   The Epidemic of Drugs and Intoxicants: The Magnitude of the Problem in the West.
2. Prof. Dr. Ayhan Songar (11.30-11.45)
   Alcohol: A social poison
3. Prof. Dr. Jamal Mazi Abul Azaim (12.00-12.15)
   Role of the Mosque in Confronting the Epidemic of Substance Abuse
4. Prof. Dr. Mahmood Abdul Jawwad (12.15-12.30)
   Changing Pattern of Drug Addiction.
5. Captain Hamad Al-Sarea (12.30-12.45)
   The Main Causes Behind the Criminals of Drug Addictions.
6. Prof. Dr. Hussain Hamed (12.45-13.00)
   The Preventive Role of the Mosque.
7. Discussions (13.00-14.30)

Break and Prayers (14.30-17.30)

THIRD SESSION:

MAIN ROOM

Time: (17.30-21.00)

Chairman: Sheikh Mohammed H. Al-Khoja

Moderator: Dr. Salah Al-Atequi

FIRST:

Report of Room One (17.30-18.00)
Report of Room Two (18.00-18.30)
Discussions (18.30-19.30)

SECOND:

PLENARY LECTURES: (19.00-21.00)

1. Dr. Sheikh M. Sayed Tantawi (19.00-19.45)
   The Need of the Medical Sciences to Jurisprudence.
2. Prof. Dr. Yousuf Al-Qaradawy (19.45-20.30)
   The absence of the spiritual values and the loss of the man due to materialism
3. Discussions (20.30-21.00)

THIRD DAY: TUESDAY, NOVEMBER 22, 1988

FIRST SESSION:

MAIN ROOM

Time: (09.00-11.00)

PLENARY LECTURES:

Chairman: Prof. Dr. Yousuf Al-Quradawy

Moderator: Dr. Najeeb Al-Othman

Speakers:

1. Sheikh Mukhtar Al-Salami (09.00-09.45)
   The Complications of the Permissiveness.
2. Prof. Yaseen Abdul Ghaffar (09.45-10.30)
   Religion and Science an outlook on Moral Values
3. Discussions (10.30-11.00)

Break (11.00-11.15)

SECOND SESSION:

FIRST ROOM

Time: (11.15-14.30)

Chairman: Prof. Dr. Ali Abdul Fattah

Co-Chairman: Dr. Ibrahim Bin Murad

Moderator: Dr. Saleh Al-Jaraiwy

Speakers:

1. Counsellor Abdullah Al-Isa (11.15-11.30)
   Ethics in Medical Sciences.
2. Dr. Abdul Fattah Shawky (11.30-11.45)
   Ethics in the Practice of the Physician.

Prayer (11.45-12.00)

3. *Prof. Dr. Hassan Hathout* (12.00-12.15)
   Document of Kuwait Medical Ethics.
4. Prof. Dr. Omar Shaheen (12.15-12.30)
   Islam and Mental Health.
5. Discussions (12.30-14.30)

Break and Prayers (14.30-17.30)

SECOND SESSION:

SECOND ROOM

Time: (11.15-14.30)

DISEASES OF THE ERA

Chairman: Prof. Dr. Ahmed Khaleefah

Co-Chairman: Dr. Abdul Hai Awady

Moderator: Dr. Adel Al-Tawheed

Speakers:

1. Dr. Nabeel Al-Taweel (11.15-11.30)
   Current Alcohol Related Problems.
2. Dr. Maher M. Hathout (11.30-11.45)
   Impact of Moral Licence on Public Health.

Prayer (11.45-12.00)

3. Dr. Helmy Wahdan (12.00-12.15)
   AIDS: "The Problem of World".
4. Mr. Hassan Yousuf (12.15-12.30)
   The Responsibility of Art.
5. Discussions (12.30-14.30)

Break and Prayers (14.30-17.30)

THIRD SESSION:

MAIN ROOM

Time: (17.30-21.00)

Chairman: Prof. Dr. Mohey Al-Deen Saber

Moderator: Prof. Dr. Hassan Al-Shazly

FIRST: Report of Room One (17.30-18.00)
Report of Room Two (18.00-18.30)

Discussions (18.30-19.00)

SECOND:

PLENARY LECTURES:

1. Prof. Dr. Ahmed Khaleefah (19.00-19.45)
   Crime: Prevention and Treatment
2. Discussions (19.45-21.00)

FOURTH DAY: WEDNESDAY, NOVEMBER 23, 1988

FIRST SESSION:

MAIN ROOM

Time: (09.00-11.00)

PLENARY LECTURES:

Chairman: Prof. Dr. Abdul Fattah Al-Sheikh

Moderator: Dr. Ahmed Al-Shatty

Speaker:

1. Dr. M. Al-Dakhakheney (09.00-09.45)
   Medicinal plants and Drugs.

2. Discussions (09.45-11.00)

Break (11.00-11.15)

SECOND SESSION:

FIRST ROOM

Time: (11.15-14.30)

APPLIED WORK IN THE ISLAMIC MEDICINE

Chairman: Prof. Dr. Mohammed Al-Dakhakhany

Co-Chairman: Prof. Dr. Attaur Rehman

Moderator: Dr. Hamad Al-Abbad

Speakers:

1. Prof. Dr. Attaur Rehman (11.15-11.30)
   Recent Advances in Medicinal plants Research.
2. Dr. Ahmed El-Kadi (11.30-11.45)
   The use of Natural Immune Enhancers in the Treatment of Far Advanced Cancer.

Prayer (11.45-12.00)

3. Prof. Dr. M.M.A. Al-Mazaar (12.00-12.15)
   Functional and Behavioural Teratological Studies of a Certain Herbal Formulation in Rats.
4. Prof. Dr. Mohammad Sabir (12.15-12.30)
   Pharmacological Basis of Therapeutic Action of a Herbal Formula in the Treatment of Chronic Bronchitis.
5. Dr. S.K. Nazimuddin (12.30-12.45)
   Effect on Experimentally Induced Ulcers of Certain Medicinal Plants Clinically Used in Rheumatoid Arthritis.
6. Prof. Dr. M. Abdussalam (12.45-13.00)
   Re-Appraisal of Muslim Food Laws.
7. Discussions (13.00-14.30)

Break and Prayers (14.30-17.30)

SECOND SESSION:

SECOND ROOM

Time: (11.15-14.30)

MEDICAL MIRACLES IN QURAN

Chairman: Dr. Abdullah Bin Naseef

Co-Chairman: Prof. Dr. Salem Najam Salem

Moderator: Dr. Ahmed Al-Duaij

Speakers:

1.	Dr. Y.N. Khawaji *Treatment of Addication by Medicated Placebo.*	(11.15-11.30)
2.	Dr. M. J. Al-Habbal *A Study of Serum and Urine Osmolalities During Ramadan Fasting.*	(11.30-11.45)
	Prayer	(11.45-12.00)
3.	Dr. O. Raslan *Honey Application in Cancer Wounds.*	(12.00-12.15)
4.	Dr. Mohammad El-Banby *Honey Effects on Surgical Wounds.*	*(12.15-12.30)*
5.	*Dr. B.A.M. Kasem* *Early-life Praying Prevents Back-ache.*	(12.30-12.45)
6.	Some Additional Papers and Discussions	(12.45-14.30)
	Break and Prayers	(14.30-17.30)

THIRD SESSION:

MAIN ROOM

Time:		(17.30-20.30)
Chairman:	Dr. Abdul Rehman A. Al-Awadi	
Co-Chairmen:	Prof. Dr. Mammdouh Gabr & Dr. Raof Shalaby	
Moderator:	Dr. Ali Yousuf Al-Saif	
FIRST:	Report of Room One	(17.30-18.00)
	Report of Room Two	(18.00-18.30)
	Discussions	(18.30-19.00)
SECOND:		
	Recommendations	(19.00-20.30)

CLOSING SESSION:

MAIN ROOM

Time:		(20.30-21.30)
Chairman:	Sheikh Jaad Al-Haq Ali Jaad Al-Haq	
Co-Chairmen:	Dr. Abdul Rehman A. Al-Awadi & Prof. Dr. Mamdooh Jaber	
Moderator:	Dr. Abd El Monem Aboul Fatouh	

INAUGURAL SESSION

REPORT *(Not available in English)*
Dr. Ali Yusuf Al-Saif

WELCOME ADDRESS *(Not available in English)*
Dr. Abd El Monem Aboul Fatouh

ADDRESS TO THE CONFERENCE *(Not available in English)*
Prof. Dr. Mamdooh Jaber

WELCOME ADDRESS *(Not available in English)*
H.E. Dr. Abdul Rahman Abdulla Al-Awadi

SPEECH *(Not available in English)*
H.E. Sheikh Jaad Al-Haq Ali Jaad Al-Haq

SPEECH FROM THE REPRESENTATIVE OF HIS EXCELLENCY THE PRESIDENT OF ARAB REPUBLIC OF EGYPT *(Not available in English)*
H.E. Prof. Dr. Mohammad Raghed Dowaidar

PART ONE

CURRICULUM OF THE FACULTY OF MEDICINE FROM THE ISLAMIC VIEWS

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CHAPTER I
PLENARY LECTURES

1. YOUTH BETWEEN INNOCENCE AND GUILT *(Not available in English)*
   Prof. Dr. Abdul Aziz Kamel
2. HERITAGE AND ITS RELATION WITH THE FUTURE PROSPECTS OF MOSLEM WORLD *(Not available in English)*
   Prof. Dr. Mohey Al-Deen Saber
3. Discussions *(Not available in English)*

CHAPTER II

CURRICULUM OF THE FACULTY OF MEDICINE FROM THE ISLAMIC VIEWS

(A) HERITAGE:

1. IMPORTANCE OF ISLAMIC LEGACY IN THE FIELD OF THE STUDY OF MEDICINE
   Prof. Dr. Saeed Al-Fatah Ashoor
2. ISLAMIC MEDICINE HERITAGE *(Not available in English)*
   Dr. Ibrahim Bin Morad

(B) ISLAMIC MEDICAL JURISPRUDENCE:

1. THE NEED OF THE FACULTY OF MEDICINE TO THE ISLAMIC JURISPRUDENCE *(Not available in English)*
   Prof. Dr. Khaled Al-Mazkour
2. AN OUTLINE OF A SYLLABUS IN ISLAMIC MEDICAL JURISPRUDENCE
   Dr. Mohammad Ali Al-Bar
3. ISLAMIC MEDICAL CURRICULUM *(Not available in English, but its Abstract included)*
   Prof. Dr. Salem Najm Salem
4. DISCUSSIONS *(Not available in English)*

Bulletin of Islamic Medicine, 5: (29-34), 1988.

THE IMPORTANCE OF ISLAMIC LEGACY IN THE FIELD OF THE STUDY OF MEDICINE

Professor Dr. Said A. F. Ashour

EGYPT

It seems that the natural approach to this research in defining "Legacy" linguistically will put us within the right framework in which we have to move. The great Arab encyclopedist Ibn Manzur says in his dictionary "Lisan Al-Arab" that the different Arab words meaning "inheritance", "heritage", "tradition" and "Legacy", all mean what is bequeathed. Legacy is inheritance, and inheritance means what is inherited. This means that legacy is what is handed down by predecessors. It is said that a man has left either money or glory for inheritors; so inheritance may be either material or immaterial.

We conclude from this definition that there is a clear concept concerning the meaning of Islamic Legacy. It means what the builders of Islamic Civilisation have left behind. Describing this legacy by being Islamic, shows that this multi-dimensional civilization was born, grew up and flourished under the canopy of Islam, with its spirit, values, ideals, conceptions and principles.

Researchers are still overwhelmed by the vastness of this legacy, especially in the fields of literature, science and art. Though researchers have made some progress in studying a part of this legacy, yet its larger part is still out of the way, waiting for studying and making use of it.

From the study of Islamic legacy in the field of Medicine, it is clear that this science in particular had enjoyed a special status among other branches of science that Moslems shared in. This status was not motivated for materialistic gains, but it was for human reasons aiming at treating patients, trying to cure and restore them to health.

We must confess that these sublime principles, that our ancestors had upheld, do not find adequate place in many parts of the Islamic community of today; at a time when materialism has become the superintendent power in a world that most of its people have relinquished many values which the good ancestors had upheld and lived happily with them. This trend was accompanied by a general decline in the Islamic Civilization. It has been subjected to contraction against the strong currents that control and direct modern civilization.

We have then to refer to the fact that it is not right to conceive Islamic civilization as falling apart and demolishing in facing modern currents. This civilization is still alive and will remain alive as long as Islamic faith - which is its main support - is alive.

The Islamic civilization has been subject to drooping not because it has not factors to continue to exist, but because Moslems have turned their backs to it; they have stopped caring for it, they no longer uphold its values and ideals. Perhaps they have been attracted by the gaudiness of the modern western civilization to neglect the ideals of ancestors.

This gaudiness, attractive as it may be, lacks a great deal of ethical values and spiritual ideals. Such ideals are the best when they are part of a heavenly religion. If we want to make our modern society a pure one, then we must make use of the ideals of our ancestors.

The legacy of Islam in the field of medical education can be divided into three areas: (1) an area concerning the scientific data, (2) another area concerning methodology of research and practising the profession, and (3) the third area relating to conduct, practice and ethics.

By scientific data, we mean the contents of the books of legacy in medicine and its riches. Moslem savants had left a large amount of data in medicine, found in several scientific encyclopaedias and many books that contain lots of knowledge in all branches of pathology, internal diseases, dermatology, eye diseases, bone treatment, fevers, as well as surgery, mental and psychological illness. The Moslem savants treated these diseases depending on observation, experiment and practice. They observed the development of every disease and considered the best means to cure it.

The scope of this paper will not allow us to review the works of Ibn-Sina, Al-Razi, Ali Ibn Radwan, Ibn Zahr Al-Andalusi and his son Marwan and Ibn Galgal ... and many other savants who shared in richening the legacy of Islam in the field of Medicine. The modern progress in Medicine does not underrate the value fo what Islamic civilization had accomplished in this field. It is true that modern medicine came up with new facts and theories that neither Moslems nor non-Moslems had reached. But it is taken for granted that modern medicine in the Christian World is based upon the knowledge of Islamic medicine. Many Arabic books written by the savants of Moslem Civilization had been translated into Latin as early as the twelfth century, and continued to be taught in the European arising universities till the nineteenth century. It does not detract from the value of these books to say that Moslem medical savants had benefited by the knowledge of other previous civilizations, especially the Greek and Indian civilizations. The role played by Moslem Savants was not only copying, imitating and preserving the legacy of others, but their role had extended to evaluating, correcting, creating and adding. In other words, they corrected many mistaken concepts and added new information that no one had known before. Thus they made medicine an established science depending more on facts rather than on assumptions, illusions and imaginations.

If the Islamic medical legacy is considered the basis on which the West has based its medical knowledge, then Moslem scientists, working today in the medical academic and non-academic fields ought to know more about this legacy. Savants in the world's greatest universities care much about studying the history of various sciences such as medicine, physics and chemistry, because it has become a fact that it is not enough for a scientist to know all modern and latest theories without having a base about the beginning and development of these sciences. Thus everything will be in the right place and the researchers can erect their building on a hard ground.

As for the field of medical studies there is an area from which scientists working in this field can avail themselves. The legacy of Islam contains some useful books written about nutrition and the elements constituting human food and the useful and harmful kinds of food. Strange results after lengthy experiments had been arrived at. It is sufficient to refer to the books written by Al-Razi and Ibn-Sina in this field.

There is enough proof that Moslem savants did not only copy from others, but they made research and experiments, made corrections and additions. Al-Razi in the preface to his above-mentioned book ("The benefits of food and protection against its harms") says that he wanted to write "a book to clarify the benefits of food, taking into account to correct the faults in which Galen-the great Greek savant-had fallen".

Thus, Moslem savants classified all kinds of food, such as corn, meat, milk, eggs, vegetables and fruits; as well as drinks and liquids. They mentioned the properties of each one, its benefits and harms. Much of this

information is repeated by modern doctors; yet some of these modern doctors know but a little deal of this kind of knowledge.

The Moslem physicians left a wide information on the description of medicines for the treatment of many diseases. They divided the medicines into three parts: vegetable, animal and mineral medicines. One of the best books on this subject is written by Ibn Al-Beitar, who says in its preface that he did not only quote what the Greek physicians - Dioscorides and Galen - had mentioned, but he "added what others said about vegetable, mineral and animal medicines; and also mentioned what later scientists and biologists had written about medicines which Dioscorides and Galen had not mentioned or known before." Thus Ibn Al-Beitar dealt with every kind of food and medicine, he explained its benefits and harms. Modern medicine cares now of many of these kinds such as lemon, barley water, anise ... etc.

Moslem surgeons used strings to sew wounds made from animal intestines, after being sterilized and dried up. These have proved to be the best kind of strings that can be used in operations; because the human body can absorb them easily, unlike synthetic strings which the body rejects as strange.

Thus, the informations and knowledge found in Islamic legacy do not only benefit modern physicians but leads them to new horizons.

As for the methodology of research, Moslem scientists considered medicine a human science. If modern scientists have arrived at a definition and a framework for every science, then Moslem scientists in the field of medicine had defined the way to examine the sick in order to find out the cause of his sickness. The Egyptian physician Ali Ibn Radwan who lived in the Fatimid epoch says:

"To know the malady, watch the members, the face, the temper and the skin of the patient. Look at the functioning of the internal and external members; for example, call someone from a distance to find out how his listening is. Test his eye sight by letting him look at far and near objects. Test his tongue by the accuracy of his articulation. Test his strength by lifting weights, catching things, walking, ... etc. You can test his bowels by inspecting his excrement. You can know about his heart by the pulse and conduct. You can learn about his liver by the urine exuded. You can test his mind by asking him about things and see his understanding and obedience to carry orders. You can know about other members by your judgement and wisdom. You may need to ask the patient to decide how gross is the symptom ..."

Thus, when we ask modern doctors to make use of the methodology found in Islamic legacy on which physicians of Islamic civilization had depended, we do not ask them to relinquish the modern scientific methods of research, and depend completely on traditional methods. It is assumed that the posterity should make use of what the ancestors had built. The main purpose for reviving the legacy is to absorb an important fact, that is: Islamic legacy encompasses a large amount of knowledge and methodological rules that modern science had made use of. So, if this becomes clear before scientists and researchers of today they will become certain that this knowledge is not mere illusion as some think. This knowledge is not hypotheses without proof as some believe. It is the outcome of lengthy experiments and research, reached by Moslem scientists after hard practices and experiences. The Europeans had adopted much during their modern renaissance, and still they develop and evolve till nowadays. It is sufficient to say that Islamic medicine had been based on observation, experiment and practice. The Sheikh President Ibn Sina says:

"Observing the patients has opened up many ways to treating the diseases after experimentation."

If modern doctors realize all this, then their look at Islamic legacy will be more equitable; and surely they will discover new benefits from this legacy; leading to new horizons.

Moslem physicians had assured that medical knowledge is not to be gained only from books, but in the

first place from experience and practice, so that a doctor can make the right diagnosis and cure. Abu Bakr Al-Razi says:

"Reality in medicine is unattainable; and cure according to books without the doctor's rationality and sensibility is dangerous".

Thus, through experience and practice, Moslem doctors could diagnose many diseases unknown to others before them. This was not achieved easily but it came by, after hard efforts. The great doctor Al-Razi was described as:

"Intelligent, witty, kind to patients, clever in curing them, working hard to find out the secrets and mysteries of the profession as well as of other sciences. He dedicated all his time and effort to read what other scientists had written".

We conclude from this that Islamic medicine did not confine itself within a narrow circle, but it extended to experiment and practice.

This was achieved by relating the study of medicine with setting what they called Bimaristans, that is to say hospitals. The study of medicine was not practised in the mosque or school, but in hospitals, where patients live a regular life, in a healthy climate, under the supervision of doctors. Learners follow up - with their teachers - the stages of every case, and try to discover the effect of medicines given to patients. Historians mention that Nour El-Din Mahmoud Ben Zanki set up a famous Bimaristan - hospital - in Damascus in the twelfth century, and provided it with a high staff of doctors and "a large number of books on medicine." This hospital was supervised by the physician Abou Al-Magd Ibn Abi Al-Hakam. Doctors used to come to him to discuss medical problems. He used - surrounded by his students - to examine patients everyday, and then to spend about three hours examining some medical books.

For every patient in Moslem Bimaristans a file was made to record his development, the course of the case whether towards the better or the worse. Kinds of food to be given to every patient were recorded; relating causes and results, using reason and assumption very cautiously. Moslem physicians did not recommend changing the doctors who treat a patient, because this will lead to contradictions and mistakes in diagnosis. Al-Razi says:

"The patient should trust one doctor only: that who applies many doctors is about to fall in the mistakes of each one of them".

A doctor is demanded to be well-cultured and well-educated, without limiting himself to his particular specialization only. Doctor Kamal-El Din Ibn Younis - a great Moslem savant in the thirteenth century had been described as:

"Wise, well-read in different branches of knowledge, great in theological subjects, reading in philosophy, medicine and education".

Al-Razi says: "That who does not care for natural phenomena, philosophy, logic; and cares only for bodily pleasures, is accused of being ignorant, especially in medicine."

It was told about the physician Abou-Al-Salt Omayyiah - a doctor from Al Andalus who came to Egypt in the Fatimid epoch - that "he had reached a high standard in the study of medicine unattained by other doctors, he was knowledgeable in literature unlike many others, he was a great mathematician without a peer, skillful in music, clever at playing the lute".

The effect of Islamic legacy on the ethics of the profession is undescribable. Islam as a revealed religion is careful about conduct and manners, so much that the Prophet Mohammed (ﷺ) has been described as being

of high manners, and that he was sent to perfect the morals of people. Since the profession of medicine demands such good manners, thus Islamic legacy is full of such teachings.

The first of these manners is kindness to the sick. The patient however rich and high ranking he is, needs cure at the hands of a kind Doctor. What, then, is the case with poor patients who suffer from pain and poverty. So the first thing that a doctor should do is not to look for material benefit. He has a right to make a living, but in merciful way without exhausting the patient. Moslem savants often said that the doctor should aim at winning God's reward, not collecting money. Al-Razi said that the doctor should be in a good condition without being eager to make money or refusing completely to have some, he should be neutral.

So, many Moslem doctors were keen to treat the poor first. Many doctors did not seek to treat the rich and rulers, so that they would not neglect their original human message. Moreover, some doctors used to help their poor patients. It is mentioned that Amin Al-Dawlah Ibn Al-Talmith, a celebrated physician, had succeeded in curing a king who sent him afterwards four thousand Dinars and a big present of horses and slaves. But the doctor refused to take anything. He said "I swear I will not accept anything, wealth is not everything". Ibn Al-Talmith refused to go to any king at his palace to treat him, but he would take care of a poor man, giving him two dinars after curing him.

The great doctor Al-Razi was described as: "generous, obliging, kind to people, merciful with the poor and the sick; giving them money". Also it was told about the doctor Abou-Al-Kheir Al-Hassan Ibn Sawar - in the tenth century - that if he was invited by a religious man, he would go to him saying "I have come to you to absolve myself from going to bad people and tyrants". But if he was invited to a king, he would put on his best costume. Thus, "he was humble with the poor and great with the great".

It was acceptable for a doctor to be proud with his patients or to be grim with them. The legacy of Islam is rich with recommendations that a doctor should meet his patients with a shining face, talking to them simply, easing their cares, inspiring hope. The doctor should be trustworthy, tender, not proud or vain; thus he would win the patients' love, so cure can be made possible. The great savant Al-Razi says: "The doctor should convince the patient that he is healthy, and wish him health even if this is not the case, because the body follows the sense and feeling".

For the doctor to be humble does not take from his status and dignity, because these are not made by rudeness and vanity, but achieved by simplicity, mercy, understanding and openness with others. It was told about the doctor Muwaffak Al-Din Abd-Al Latif Al Baghdadi - a contemporary of Saladin - that he used to advise his students and contemporary doctors by saying:

"Never be harsh when talking, or rude in discussions because this spoils the temperament of the body and indisposes the mind. Do not be proud and do not degrade yourself so that you will be looked down upon".

A doctor should not be in hurry to examine his patients. A better job is done when one is not in a hurry. One of the prophet's (ﷺ) sayings often quoted in this respect is

"God likes that he who does a work ought to perfect it".

Thus, it was said, "A doctor should inquire the patient about everything before rendering his judgement". The scientist, physician and philosopher Al-Kindi says in his advice:

"The doctor should fear God and not endanger souls which cannot be substituted. As he likes to be mentioned that he has succeeded in curing the sick, he also must beware of being accused that he is the cause in damaging a person's life leading him to death. The reasonable should know that there is better knowledge above his standard, so he should be humble. The ignorant is the one who thinks himself as knowing everything. This will bring hatred upon him".

It does not detract from a doctor's rank to seek others' experience. Above every savant there is a superior one. It is mentioned in history that when the Abbassid Khalif - Al Nasse Le-Din Allah - fell sick at the beginning of the thirteenth century, a very big staghorn was discovered in his bladder. The chief surgeon who was sent for to make the operation for the Khalif said after examining him "I need to consult some skilful doctors on this matter".

A part of the behaviour of the Moslem doctor is that he should not with-hold his knowledge from his students. He had to acquaint them with all the knowledge he has attained, following the Prophet's (ﷺ) saying:

> *"Spread knowledge. Continue teaching till all are acquainted. Knowledge perishes when it becomes secret".*

If a student excels his master, this will be an honour to the master himself. The savant Radie Al-Din Al-Rahby - a contemporary to Saladin is said to have many doctors, some of them excelled him.

When a doctor practises the profession before his students, he should uphold the ideals of behaviour and manners to be always their model and example.

Related to this is that teaching medicine should not be a job from which the master gains money from his students. It was told about the doctor Fakhr Al-Din Al-Mardini - who excelled all his contemporaries in philosophical sciences - that he spent sometime in teaching medicine in Damascus. When he came to leave the city in 1193, one of his students offered him a sum of money to stay - another period in Damascus to learn more from him. The master rejected the offer and said: "Learning is not for sale".

Finally, every patient has his own secrets that should not be revealed for no other one but the doctor. The doctor should be confidential so that no moral harm will hurt the patient. Moslem doctors were keen on keeping the secrets of the patients to protect their interests and dignity.

The Egyptian doctor Ali Ibn Radwan, who lived in Cairo during the Fatimid epoch, and was appointed chief physician by the Khalif Al-Hakim, said:

"A doctor, according to Hippocrates, is the one who combines seven qualities:-

1. He should be good-mannered, well built, smart, sensible, reasonable, having a strong memory and polite.
2. He should be well dressed, good smelling, clean in body and dress.
3. He should be confidential, letting out no secret of his patients.
4. He ought to have a stronger desire to cure the poor sick rather than treating the rich.
5. He must be keen on teaching and helping people in every possible way.
6. He should be good-hearted, polite, truthful. He should not care for whatever women matters or wealth he might have seen in the houses of the patients. He should not try to touch anything.
7. He should be trustful, caring for souls and wealth of his patients. He should not prescribe a fatal drug, or a medicine that would cause miscarriage. He should treat his enemy with good will.

The teacher of medicine profession is the one who could combine these qualities after perfecting the profession itself. The learner is the one who can be judged as good-mannered and keen on learning, intelligent and remembering what he has learned".

This is the actual perspective for anyone who wishes to practise the profession of medicine from a well established Islamic legacy.

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AN OUTLINE OF A SYLLABUS IN ISLAMIC MEDICAL JURISPRUDENCE

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INTRODUCTION:

Islamic medical jurisprudence is not forensic medicine given Islamic label. It certainly includes a lot of forensic medicine, but it is not limited by it.

It also includes a lot of medical ethics. Phenomenal advances in medicine especially in the last two decades have made the old medical ethical codes obsolete in many ways.

The sole aim of medicine was to cure disease, mainly physical disease. Now medical techniques are called upon for purposes which are not directly related to the health of the individual patient e.g. in relation to contraception, abortion, sterilization, plastic surgery and choice of sex. There is a widening of the doctor's role into the social field.

On matters of life and death, sexual morality, abortion, *in vitro* fertilization, sperm, egg or embryo donation, surrogacy and genetic counselling, a clamour of opposing opinions arise from different camps in different countries.

There is no consensus of opinion in such matters, even among doctors. The lawyers, members of parliaments, clergy, the media and the public at large are all discussing these hair - raising contentious subjects.

It is, therefore, of paramount importance for the practising Muslim Physician to know, at least the basic Islamic rules that regulate his profession.

It is true that new methods and techniques in medicine have no precedents, and therefore make it difficult for Islamic jurists to give clear cut rulings. However the jurists were very active in the last five years, and they held many conferences, to which many doctors were called, to discuss issues such as brain death, abortion, contraception, milk banks, artificial insemination, *in vitro* fertilization and surrogacy.

This is an unexpected feat, which would greatly help to formulate the rules regarding medical ethics in the arena of rapidly advancing medicine of high technology.

This paper will discuss the outlines of a syllabus in Islamic medical jurisprudence, in a perspective of a wider curriculum of Islamic medicine, that we suggest to be taught in schools of medicine in Islamic countries.

The Objective of the Syllabus in Islamic Medical Jurisprudence:

This syllabus aims at graduating a Muslim physician who knows and practises the Islamic rulings

regarding health and disease, and who is capable of instructing his patient, according to his knowledge in medical sciences and its Islamic rulings.

This study should include the following:-

1. The Islamic rulings related to the acts of worship during the course of illness e.g. purification (Taharat), prayers, fasting, etc.
2. The Islamic rulings that regulate medical practice and its ethics.
3. The Islamic rulings that regulate new medical achievements.

Contents of the Syllabus:

A syllabus in Islamic medical jurisprudence should contain a study of the following two main items of Islamic jurisprudence, as a brief out look, with more detail to those aspects related to the practise of medicine and its ethics.

Islamic jurisprudence is divided into following items:

1. *O'sool (fundamentals, basis)* which formulate the basic sources of Islamic laws, and how they are arrived at. It is important for the practising physician to know how new rules for new problems arising in the community, (here in the field of medicine) are arrived at. If he has a fair idea about *O'sool,* he would appreciate these rulings arrived at by the jurists. He may as well be competent enough to understand and even participate in the dicussions of the jurists to arrive to new rulings in newly discovered medical techniques, that encroach on human life and morality.
2. *Foroo'* ie. Branches of Islamic jurisprudence which include the details of every aspect of life and worship *(Ibadat and Muamalat).* The practising physicians need to know things related to his profession. Therefore, the syllabus should contain subjects pertaining to the day-to-day problems faced by the practising physician. Things not related to the profession should not be included, or if included should be studied very briefly.

The medical student is already facing a huge amount of knowledge to study, and there is little time left in the curricula for a new addition that takes time and effort to study. Therefore, the syllabus we suggest should be as short as possible, without affecting pursuing the aim of the syllabus.

Contents:

1. *Study of the basic rules (Qawa'd) and Osool (fundamentals) of Islamic jurisprudence especially those related to the practice of medicine.* It is important to stress here the fact that the Islamic law *(Shari'a)* is part and parcel of Islamic religion. Islam is not only acts of worship, or moral codes, it is mainly a way of life.

The basic rules of Islamic jurisprudence are already defined and compiled by the Islamic jurists and fundamentalists *(Osolyoon).* The first man who laid these bases clearly was Al-Imam - Al-Shafi in his treatise *'Al-Risalah'* in the second century of Hijra (150-204 A.H).

The main sources of Islamic Law *(Shari'a)* consisted of:

(i) *The Holy Quran*
(ii) *The Sunna:* (The trodden path) which includes the sayings of the Prophet Mohammed (ﷺ) which is

known sometimes as the *(Sunna Qawliyya)* or *Hadith,* the deeds and acts of the Prophet (ﷺ) *(Sunna Feliyya),* and approvals *(Sunna-Taqririyya)* whether they are expressed or implied.

(iii) *The Qiyas:* or *Ijitihad* whereby the jurists or Kadi (judge) would use analogy and reasoning to arrive at the judgement which is not mentioned in the holy Quran or *Sunna.*

(iv) *Ijma:* This is the consensus of opinion of jurists. True *Ijma* of the whole community of jurists all over the world was always difficult to achieve. However the consensus of the majority of opinions is more realistic one. Some jurists would limit *Ijma* to the era of *Sahaba* [companions of the Prophet(ﷺ)], others will extend it to all ages.

There are other sources like *Almasaleh Al-Morsalah* which is held by Maliki School. It simply means taking care of public interest, provided it does not clash with a clear text of the Holy Quran or *Sunna.* The Hanafi School has a similar source which they call *Istihsan* i.e. seeking the best solution for the general interest.

2. *Study of Foroo' (branches) of Islamic Jurisprudence which are related to the patient and his ailment or to the practise of medicine.* These will include the following:

The rules regarding *Taharat* (cleaning) and *Najasat* (dirt) which will involve human excreta and secretions such as semen, menses, vaginal discharge, uretheral discharge etc.

The rules regarding the cleaning *(Tharat)* for those suffering from anal fistulas, vaginal fistulas, colostomies, incontinence and those having to put dressings for their wounds or plaster of paris for their fractures, should all be studied.

The rules regarding the prayers *(salat)* of the sick and the disabled should be studied.

Similarly the rules regarding fasting of the sick; when he should stop fasting and when he is allowed to fast? Is it allowed to give injections (i.m, i.v) during fasting? Is it allowed to give blood for laboratory tests, or blood donation during fasting? Can the patient receive blood if he is fasting? etc. Can the pregnant lady or that who is breast feeding fast?

The rules of Haj and their application to the patient should be studied. The use of the pills to delay menses in order to perform Haj or fasting should also be studied.

The rules regarding treatment and using prohibited medicaments e.g. alcohol in medicine, drugs derived from porcine origin e.g. porcine insulin or porcine enzymes, or even porcine valves for heart-valve replacement.

Similarly the rules regarding examining the opposite sex and examining the sensitive parts called *"awra",* should be studied.

The rules that control the medical ethics and medical practice and litigancy between the patient and the doctor should be studied with sufficient detail, as to give the student fair knowledge of the Islamic rules that regulate his daily practice.

A fair idea of the Islamic rules regarding *"Halal"* and *"Haram"* food and drink should be given to the medical student. He should also know, at least in general terms, the rules regarding the slaughter of animals.

The Islamic rules that regulate marriage should be studied in general terms. Premarital medical counselling and examination is a pre-requisite in many Islamic countries to perform the contract of marriage. Genetic counselling, rules regarding the duration of pregnancy, rules regarding the rights of the fetus and embryo and the Islamic rules regarding breast feeding and nursing of the baby should all be studied in fair detail.

Sexual practices and their Islamic rules should be studied. Premarital, extra-marital relations, sexual perversions, homosexuality and rape should all be studied from Islamic perspective.

The most important of Islamic medical jurisprudence may be the rules regarding the new methods and techniques provided by the tremendous advances in medicine and moral changes of societies.

The sanctity of human life rules out the demand for euthanasia whether passive or active. However the heroic measures, sometimes practised to prolong the process of death, are not part and parcel of the subject of euthanasia.

The Islamic rules regarding contraception, sterilization and abortion should be carefully studied.

Similarly the Islamic rules regarding autopsy and postmortem dissection of corpses, organ transplantation should also be studied in some detail.

The Islamic rules regarding new methods of procreation e.g. artificial insemination, *in vitro* fertilization, donation of sperms, ova(eggs) or embryos, with ensuing formation of such banks as semen banks, egg banks or embryo banks, should all be studied in detail.

The Islamic rules regarding plastic surgery and transformation of sex, rules regarding the hermaphrodites (true or pseudo) should all be studied.

The subject of brain death received a great concern from Islamic jurists who studied it fully in three consecutive conferences and henceforth gave their rulings. These should be studied carefully by the medical students and practicing doctors.

Congenital malformations of the fetus, and hence whether to allow abortion or not, was the subject of many conferences held by Muslim jurists. Their rulings should be studied carefully and applied universally in Muslim countries.

Genetic Engineering and the rules regarding medical research and experimentation on animals or humans should be carefully studied. Problematic issues such as growing embryos *in vitro* for the purpose of study of hereditary and congenital diseases or for use as spare parts for organ transplantation for needing patients should all be scrutinised in an Islamic perspective.

ISLAMIC MEDICAL CURRICULUM

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ABSTRACT

Faith is the main pillar of Islamic Medical Education. It should be deeply rooted in medical students and well emphazised in scientific curriculum of medical schools. Allah is the creator and owner of human beings who should follow His mighty instructions in every aspect of human life.

The following facts of Islamic philosophy that must be kept in mind when medical education is to be discussed are:

1. Islam urges moslems to achieve up-to-date knowledge from anywhere, including medical sciences and by so doing they worship Allah.
2. Cure of diseases is by Allah but physicians must manage the patients with utmost best of their knowledges.
3. Prohibited stuff such as alcohol.. etc must be excluded from medications.
4. Arabic language is so rich and able to meet the requirements of medical teachings.
5. Freedom, "Shareha", Justice, Equality, Prosperity and bread youth especially medical students.

The present medical curriculum of Al-Azhar medical school Cairo include Islamic sciences beside the standard medical curriculum similar to other Egyptian Medical Schools; Medical students receive 450 hours (200 H. Fekeh, 125 H. Quraan, 50 H. Faith, 25 Tafseer, 25 H. Hadith, 25 H History") distributed over the first 4 years of medical study period.

Such sciences are not closely related to medical profession and are delivered as lectures by non-medical specialists.

In order to achieve the beneficial effects of the spirit and conduct of Islam, it is suggested that Islamic principles and teachings should be incorporated in the classic scientific curriculum, taught by well informed and Islamically oriented teachers.

CHAPTER III
PLENARY LECTURES

1. THE NEED OF THE MEDICAL SCIENCES TO JURISPRUDENCE *(Not available in English)*
   Shaikh Prof. Dr. M. Sayed Tantawi
2. THE ABSENCE OF THE SPIRITUAL VALUES AND THE LOSS OF THE MAN DUE TO MATERIALISM *(Not available in English)*
   Prof. Dr. Yousuf Al-Qaradawy
3. DISCUSSIONS *(Not available in English)*

CHAPTER IV
MEDICAL ETHICS

1. ETHICS IN MEDICAL SCIENCES *(Not available in English)*
   Counsellor Abdullah Al-Isa
2. ETHICS IN THE PRACTICE OF THE PHYSICIAN *(Not available in English)*
   Dr. Abdul Fattah Shawky
3. DOCUMENT OF KUWAIT MEDICAL ETHICS *(Not available in English)*
   Prof. Dr. Hassan Hathout
4. ISLAM AND MENTAL HEALTH *(Not available in English)*
   Prof. Dr. Omar Shaheen
5. DISCUSSIONS *(Not available in English)*

PART TWO

EPIDEMICS OF THE ERA

CHAPTER I
PLENARY LECTURES

1. COMPLICATIONS OF THE PERMISSIVENESS *(Not available in English)*
   Sheikh Mukhtar Al-Salami
2. RELIGION AND SCIENCE - AN OUT LOOK ON MORAL VALUES
   Prof. Dr. Yaseen Abdul Ghaffar
3. DISCUSSIONS *(Not available in English)*

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RELIGION AND SCIENCE AN OUTLOOK ON MORAL VALUES

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The original title of the abstract was "The Moral Aspects in the Doctor's Life". However when I began writing the text, I found myself gradually and irresistibly driven into a discussion on the relation between Religion and Science. When I finished the text, I discovered that the title was rather alien to the text. Nevertheless, I felt that a discussion on the relation between religion and science in our contemporary society is both more appealing and relevant to a conference on "Islamic Medicine" as the present one than a mere focus on "Moral Aspects in the Doctor's Life". The title had to be changed accordingly.

1. Relation between Religion and Science

Religion and Science are now generally looked upon as separate and mutually exclusive realms of human thought (whose presentation in the same context leads to misunderstanding of both scientific theory and religious belief. Scientific theory and religious belief are even seen by many to be antagonists locked in a battle to the death (R. Hooykaas, 1972)[1]. This, however, could not be actually the case as will be seen from the following discourse.

2. Religion and Science Contrasted

All human actions and behaviour imply conscious or subconscious urges, desires and compulsions which motivate them. Like everything else in life, they have causes, which one may or may not be able to analyse, but which fully justify the old dictum:'ex nihilo nihil'. Scientific research rests upon the urge, the drive, whatever one likes, to uncover the laws of the universe. The religious or metaphysical quest rests upon desires, impulses or urges to understand the universe and life not in terms of pragmatic, experimental knowledge, but in terms of experience which satisfies the natural rationality of man (Jospeh Chiari, 1977)[2].

Methodology thus diverged. While science rests on the study of the laws of nature through objective experimental approach, religion counts on personal "experiences" in man's life.

The contrast between religion and science particularly in terms of beliefs could thus be envisaged as the long echoed expressions of supernatural versus natural, materialism versus spiritualism.

3. Limitation of Religion and Science

The ever changing scientific concepts are an appalling attribute of science. "Uncertainity" and Einstein's "Relativity" are major limitations to the scientific enterprise today. Likewise, religion has its prime limitation in "Subjectivity".

4. Intentions of Natural Science and Theology

From social and anthropological viewpoints we can discern an intention which is common to both the religious and scientific enterprises and which can still be discerned today even in their present sophisticated forms-namely, their search for intelligibility, for what makes the most coherent sense of the experimental data with which they are each concerned. What proves to be intelligible is applied in science to prediction and control (if we concur with Habermas[3] and Hesse[4]); in theology, to provide moral purpose and personal meaning; and in both (if we concur with Burhoe and Campbell[5]) to social survival. Even so, the primary objective of both enterprises is to go on pressing the question "Why?" to its intelligible limits. Science directs this question to the causal nexus of the natural world. Very frequently it can provide answers to the question "Why?" which are, if not verifiable, at least falsifiable. Nevertheless, a scientific hypothesis of better explanatory power than hitherto is sometimes adopted even when no empirical tests can be devised which would directly falsify it, as T.S. Kuhn's account[6] of certain historical turning-points in physics makes abundantly clear, even if it cannot be generalized to all the sciences (certainly it is hard to see the history of chemistry and biochemistry in this light).

The religious quest, or rather, the theological enterprise, as I would prefer to call it (in order to stress that we are, for the moment at least, concerned with the intellectual aspects of religion), equally presses the question 'Why?' until, as J.J. Shepherd[7] puts it, 'to press it further is plain silly' (A.R. Peacoke, 1978)[8].

Thus, while science concerns itself with the phenomena of the universe, religion concerns itself with the universe itself.

5. The Relevance of Religion and Science

It is generally recognized that science has arisen and developed as a consequence of a stimulus to human thought by the perspective of creation which religion has presented in the divine books (R. Hooykaas, 1972)[1]. In this contex, monotheism and deidefication of nature, a basic doctrine in religion have encouraged man to override nature and explore its resources for his own benefit. This has been the start of the rise of natural science which gradually developed into modern science (Joseph Chiari, 1977)[2]. As Hooykaas puts it "Metaphorically speaking, whereas the bodily ingredients of science may have been Greek, its vitamins and hormones were religious.

6. The Two Books

Religion and science could be metaphorically described as the "Book of Scripture" and the "Book of Nature", the two books by which God has made Himself known to man.

7. The Need of Science to Religion

In the first place, there is a growing realization of the tenuous and fragile connection between investment in pure research and economic growth; of the alarm about pollution; of well-publicized cases of the unpredictable and unexpected effects of the increasing use of drugs in medical therapy; and, supremely, of the nightmare possibility of nuclear warfare and of perpetual contamination from the use of nuclear energy — the bitter fruits of one of the most creative epochs of the human intellect, the great paradigmatic shifts in the concepts of physics in the early decades of this century. Thus, whether they have liked it or not, scientists across the whole spectrum of their activity - at first the physicists, then the biologists and medical scientists, and now more recently, to their particular surprise, the chemists and the molecular biologists — have all come face to face with baffling ethical problems and the possibly dire social consequences of, at least some, of their apparently "pure" research (A.R. Peacoke, 1978)[8].

In the second place, wars and regional conflicts are now witnessed all over the world, a testimony against science that it has failed to provide peace to this boiling world.

In the third place, as much as science has disregarded the inner aspect of man, man's tension and dissatisfaction has been a present day feature of life everywhere.

8. The Need of Religion to Science

"BEFORE THIS WE WROTE IN THE PSALMS AFTER THE MESSAGE (GIVEN TO MOSES): MY SERVANTS, THE RIGHTEOUS, SHALL INHERIT THE EARTH"

(S.21:V.105)

Science is Power. Power has been called upon by Islam to help circulating its scheme and overriding its opposers.

Science can be envisaged to be the means whereby the promise of God can be fulfilled.

"AGAINST THEM MAKE READY YOUR STRENGTH TO THE UTMOST OF YOUR POWER, INCLUDING STEEDS OF WAR, TO STRIKE TERROR INTO (THE HEARTS OF) THE ENEMIES OF GOD AND YOUR ENEMIES".

(S.8:V.60)

Natural science as disclosed through its fascinating discoveries has revealed to man, the creature, the beauty of the universe and the all-embracing wisdom and power of the creator.

"The Grand Design" (Kurt Mendelssohn, 1976)[9], "The Music of Creation" and "The Dance of Creation" (A.R. Peacoke, 1978)[8] are terms which have been voiced repeatedly by the most leading scientists.

9. The Need of Islam to Science

The dangers to which Islam, as a religion, is exposed today are perhaps greater than any that it has faced in the past. The most potent come from those forces which have undermined, or threaten to undermine, all theistic religion. The external pressure of secularism, whether in the seductive form of nationalism, or in the doctrines of scientific materialism and the economic interpretation of history, has already left its mark on several sections of Muslim society (H.A. Gibb, 1980)[10].

A prudent indulgence in science may be the remedy of this situation.

10. A Hope!!

The recent classic studies of Nobel Prize Winner, Roger Sperry on interactions of brain and mind, may seem to cast a beam of light on the "No-Man's Land" between religion and science namely the human mind.

Scientific research along such lines may hopefully tend to bridge the gap between religion and science as Sperry himself puts it. "In the context of today's mounting global problems and in the absence of population controls the relative long-term social benefits from advances in science and technology are diminished. At the same time the human value spin-offs from the mind-brain and other sciences are thrust into a strategic position of top concern because of their key role in the search for ultimate criteria for policy priorities and decision-making guidelines. Recent conceptual developments in the mind-brain sciences rejecting reductionism and mechanistic determinism on the one side, and dualism on the other, clear the way for a rational approach to the theory of values and to a natural fusion of science with ethics and religion. Science can be upheld as the best route to an increased understanding and rapport with the forces that made and move and

control the universe and created man. The outlines for a global ethic emerge that would promote a reverent respect for nature and for the evolving quality of the biosphere and in which, the well being, further development and sanctity of the human psyche stand out as the foremost, but not sole, concern. Such values, if implemented, would set in motion the kind of social changes needed to lead us out of the vicious spirals of worsening world conditions. For our children's children, averting nuclear war won't help much if the population bomb and other global threats continue unchecked" (Roger Sperry, 1983)[11].

In this context, I should refer to Sheikh Al-Ghazali[12], the great theologian of Islam, who categorised human mind into four types. The first is a mind whereby man acquires the skill of manual work in agriculture and industry and differentiates man from animal. The second is a mind which provides man with reasoning. The third is a mind which confers on man's knowledge gained from experiments and experiences. The fourth is a mind which precludes evil actions. It is obvious that this fourth mind is the ultimate form of human mind which is equivalent to the mind Sperry is seeking. In Sheikh Al-Ghazali's terms, each mind stems from the precedent one and gives rise to the next. It seems as if he has been hinting at "evolution".

In the light of the present discourse, scientists, theologians, philosophers and doctors might find a formula for reconciliation of religion and science.

In the medical profession where moral values are foremostly wanted such a reconciliation may enable a rational approach towards the ever appearing problems in medical practice consequent on the perennial developments in the medical sciences as well as a sound formulation of medical ethics.

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CHAPTER II
PAPERS PRESENTED

1. THE EPIDEMIC OF DRUGS AND INTOXICANTS: THE MAGNITUDE OF THE PROBLEM IN THE WEST *(Not available in English, but its Abstract included).*
   Dr. Ahmed El-Kadi
2. ALCOHOL : A SOCIAL POISON
   Prof. Dr. Ayhan Songar
3. ROLE OF THE MOSQUE IN CONFRONTING THE EPIDEMIC OF SUBSTANCE ABUSE.
   Prof. Dr. Jamal Madi Abul Azayem
4. CHANGING PATTERN OF DRUG ADDICTION *(Not available in English, but its Abstract included)*
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5. CAUSES OF RECIDIVISM IN NARCOTICS CRIMES
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7. DISCUSSIONS *(Not available in English)*

THE EPIDEMIC OF DRUGS AND INTOXICANTS: THE MAGNITUDE OF THE PROBLEM IN THE WEST AND ITS CAUSES

Dr. Ahmed Elkadi

U.S.A.

ABSTRACT

The increasing use of narcotics and alcohol in the United States has reached epidemic proportions. Tens of millions of addicts are wasting tens of billions of dollars every year. In addition to the wasted money, moral values, health, and lives are being destroyed. The failure of the United States to cope with this problem testifies to the ineffectiveness of the used measures and the need for alternative ones. Analysis of the problem shows that several factors are responsible. On the part of the suppliers there is an indiscriminate greed for money and power, lack of fear of consequences, and lack of ethical or moral values. On the part of the consumers there is lack of effective positive motivation and involvement, lack of resistance to the temptation, and a presence of bad companions.

A comprehensive Islamic approach which addresses all these factors will be presented and discussed. It will be apparent that such an Islamic approach can make the difference between failure and success in the control of this most serious medical and social disaster.

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ALCOHOL AND DRUG ADDICTIONS SOCIAL POISONS

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It is unfortunate to say, today's so called "modern community" regards alcohol and some drugs, the social poisons, as a normal and acceptable phenomenon when taken within certain limits, which in fact makes no difference regardless the quantity taken. We must first of all, emphasize the point that using alcohol and other toxic substances, for purposes of either relief or fun, is a pathologic behaviour and falls under scope of psychiatry, even if they are taken in minor quantities. Today's human beings, who try to make their life more colourful with a few sips of alcohol are indeed psychiatric problems. The vast progress in technology and replacement of civilization with technique, thus leaving spiritual values by the comfort of such technological facilities, increase the social stress in the society more and more. Certain groups, being well aware of this fact, exploit alcohol and drugs both as a profit making commodity and a weapon to ruin the society, its moral virtues and nations.

Within the Islamic World, no permit is granted to use alcohol even at the so-called "acceptable level", but, unfortunately, some perverted habits of the so-called "civilized and developed world" can easily be welcomed in the Islamic community. Religions adopted certain attitudes towards these social piosons and, especially in Islam religion, many qualifications which make us "human" are clearly described. For a community which really practices Islamic rules, alcohol must be out of question. But, as I have already mentioned above, alcohol is favoured by some individuals at times when spiritual values are weakened.

Following the First World War, a law named "Prohibition of Alcoholic Beverages" was passed in Turkey. But, it was later abolished as the law of prohibition of alcohol of the U.S.A. Today in Turkey alcoholic drinks are not prohibited. However, the Islamic belief and traditions make us not tolerate alcoholic drinks. As I already explained above, alcohol lies behind many crimes, traffic accidents, violation of laws, divorces, etc. either directly or as a motivating factor.

Although alcohol and other habit-creating substances show similar characteristics in principle, alcoholism has a peculiar place since it has - in some extent - acception in modern communities and since governments permit its manufacture, sale and consumption officially. In fact, consumption of drugs was prohibited in the Western World since 1916 when the "Harrison Narcotic Act" was passed in the USA. Therefore, we deem it appropriate to analyse these two different types of addiction under separate headings.

ALCOHOLISM

The Alcoholism Committee of World Health Organization defines alcoholism as "the habit to use alcohol continuously and in excess amounts beyond limits approved by traditions". Alcoholic person, on the other hand, is described as "the person whose wish to use alcohol is as much as to damage his psychological and physical health, his social, business and family relations as well as his social and economic status". Since

alcohol is strictly prohibited in Islamic communities by the order of Allah, such a pathological attitude must not even be tolerated. So, the definition of WHO deviates from principles of our religion. However, I wish to handle the matter in the today's reality that "there are those living on the earth not believing that alcohol is forbidden by religion". As a matter of fact, *Jellinec,* one of the researchers dealing with alcoholism, finds definition of WHO insufficient. He defined alcoholism as "habit to use alcohol of any kind damaging the individual or the society or both". This definition suits more to our views and understanding. In fact, alcohol in any quantity and type, damages both the individual and the society. Alcoholism is not an "individual phenomenon" as thought or as viewed by some western researchers. Alcohol dependency is a psychological destruction, a physiological addiction and loss of voluntary control. *Gordon,* emphasizing much importance on the social aspect of the matter, tries to draw a definition by asking the question, "Is there any single case, in which you fully succeeded to stop alcoholism and make the subject live in peace?..." Unfortunately the reply to this question is almost always "No!..". Because, the community in which we live, labeled "MODERN" is loosing the moral and spiritual values day by day, becoming more satisfied with the material values. The today's man, living in a sort of "toy-land", having the conceptual conflict so much as to view "civilization" and "technology" as equal to each other, will naturally use drugs and push himself into the world of phantasy, in case any small wish of himself is not fulfilled. Thus, he will refer to remedies to remove himself from the realities. In this way, alcoholism and drug addiction are getting more and more widespread, attaining very critical dimensions. *Gordon* views the matter as a "COMMUNAL DISEASE" and considers it in the same category as other contagious diseases.

Impact of various factors as social level, religion, age, sex and ethnical groups upon alcohol epidemiology is very appearent. *Horton* indicated the correlation between the level of stress and consumption of alcoholic drinks in his study conducted in 56 developing countries. He then drew his theory known as "anxiety-counter anxiety". But, even this researcher failed to reply the question why people in such countries did not prefer sports and artistic activities insted of alcohol? *Field,* cites the following psycho-social factors as the reasons of alcoholism, by his test named "cross-cultural rating score":

— decrease of the male's authority in the family,
— too much increase of the male's authority in the family,
— distortion of community-family relations.

On the other hand, *Borry, Buckwald* and *Bacon* handled the matter within the group of countries known as "developed countries", indicating that preventive measures must be taken at childhood and that a regular relationship between the child and the other members of the family is of utmost importance. Also, advertisements and motivating publications have a great impact. It is not logically acceptable for a state to tolerate his own people's intoxication while improving his economy.

Why they are drinking?... The psychological factors lying behind alcoholism are summarized as follows:

Those drinking to be strong

Such people always feel inferiority. Most of them are not aware why they use alcohol, though they somewhat know it, in order to establish an accurate relationship with others.

Those drinking for relaxation

Drinking in order to get rid of their psychological inhibitions and stresses.

Those drinking against a suppressed feeling or idea

In this case, alcohol is mostly a tool of sexual satisfaction. It happens beyond awareness. Most of them drink under the pressure of homosexual feelings and pains.

Those drinking to neutralize

These people drink to suppress their fears and problems. Most of them are affected by their obsessive-phobic feelings. I know many who drink before travel by train or aircraft in order to suppress their fears.

Those drinking to escape

They drink to escape from responsibilities of daily life and their family.

Those drinking to suppress their aggressive and antagonistic feelings

Here, impulsive feelings are suppressed by alcohol and motor impulsion is transferred to it.

Those drinking to lower their social status to a more suitable and accessible psychological level for them.

When these people get drunk, they become childish and seek for affection and love. This is the indication of a regression. This can be compared with the schizophrenic regression.

As seen, drinking habit is a psycho-social disorder regardless the level and amount. We must remove the personal and social reasons leading to it.

Finally, I wish to talk on attitudes of various religions towards alcohol.

In the *OLD TESTAMENT,* it is prohibited to eat meat of some animals, primarily pork. But there appears no prohibition for alcohol. On the contrary, words to appraise the trade of alcoholic drinks existed in the Old Testament. While studying this, we must consider that the existing copies of the Old Testemant sent to Moses is already lost. In CHRISTIANITY, wine is considered a sacred item, representing blood of the Jesus. In this context, while wine was being drunk in religious ceremonies as a symbol, being drunk is not tolerable by fanatic christians, though not expressly mentioned.

ISLAM has radically solved this matter. Mohammed (ﷺ) and Abukabr (رضي الله عنه) never used alcohol even before Islam. Prohibition of alcohol by the order of Qoran was gradual. First the 219th Verse of Bakara Surah, saying that

> *"WINE AND GAMBLING ARE GREAT SINS; SINS OF WHICH ARE GREATER THAN THEIR LITTLE BENEFITS"*

was sent. Then by the 43rd verse of Nisa Surah, it was prohibited stating that

"....DRAW NOT NEAR UNTO PRAYER WHEN YE ARE DRUNKEN....."

Finally, in 90th verse of Maida Surah, drinks, gambling, idols and fortune telling arrows were prohibited, removing from the Islamic religion. Since "there is no religion but Islam", this order of Allah is valid for all human beings!....

Here, I wish to tell a few words to the Moslems who drink from time to time, defeated by their desires. Performance never means to be exciled from the religion. A Moslem, doing what is prohibited by religion, does not lose his properties as a moslem. He is still moslem, but now he is a sinner. Repentance is always possible, provided he does not deny the sin and the order of ALLAH!...

Following these verses, our Prophet Mohammed (ﷺ) clarified the matter with his deeds:

> *"Anything causing to drunkenness is prohibited, and anything prohibited when taken in big amounts is still prohibited when taken in small amounts..."*

As seen, the Islamic religion leaves no chance for alcohol at all. If we take alcoholism as a "disese", it may again be solved within context of our belief. As our Prophet (ﷺ) said

> *"every disease has been created with its cure, except getting old, and, getting healed up is what is ordered by Allah"...*

DRUGS

Drugs are considered tools of offence for long years, as we already mentioned above. In fact, emerge of Opium as an item for drug-addicts, which was known and used as a medicine for thousands of years, is not very old. For example, the Firm Bayer of Germany presented Heroin as a medicine against coughs in 1896. On the other hand, Morphine was being used to relieve pains during the American Civil War. Only after intervention of various under-ground organizations into the matter, these items spread our world widely and became a great peril for communities. Today Opium alkaloids and other drugs travel world-round making their users either a mentally disordered person or a murderer.

Though many of such bad habits are associated with sociopathic personality, neurotics and psychotics are inclined to use drugs due to their affective problems. Many of the users are those with immature ego and super-ego having a personality dependent on others. The abnormal taste of pleasure and lack of success within the social environment of psychopathic persons lead them to drug addiction as a tool of quick emotional satisfaction. Here I want to emphasize the important role which "motivation" and "deceipt" play. The youth should never forget that, in most cases, using of such drugs once only means a life-long addiction and dependency. On the other hand, opium and other drugs were used from time to time as political tools and weapons. But, whatever the case is, the problem associated with drugs is not conceived as big as the alcoholism, in spite of the great peril it offers, and a "social tolerance" has always been existent for such items, for long a time.

Another group is the addiction to psychotropic drugs and tranquilizers. To me, this is more a problem of us, the physicians, rather than the users. If we do not prescribe medicine more than needed, and if we do not exceed dosage and treatment time and, certainly, if the medicines are used under strict control and supervision of doctors, possible perils will naturally be prevented before they emerge. In my country it is a legal requirement to prescribe psychotropic drugs on special attested and registered sheets with serial numbers, issued by Government. After becoming into force of this legal requirement, addiction to psychotropic drugs dropped almost zero.

We can summarize the problem as follows:

The causes of alcohol and various drug dependencies can be grouped in three main categories: environmental factors, personality characters of individual, and dependency creating ability of a certain drug. Especially, the weakening of moral values and religious beliefs, and the other hand, advertisements, motivations and encouragements are main causes of the widespreading of the problem. Among psychological problems of the individual who is the target of the offence, various subconscious conflicts, especially identification crisis, hidden, perversed sexual desires, repressed agressive feelings, anxiety and stress must be taken into consideration. Preventive measures are more important than the therapeutic facilities. Governments must use every media in order to create an awareness of the people against alcohol and drugs.

Every kind of advertisement of these substances must be prohibited by the governments. Alcoholic beverages must not be taken into consideration as a part of national economy. I am inviting all medical persons of Islamic world to exclude every alcohol containing medicine from their prescriptions. We must not forget the words of our beloved Prophet Mohammed (ﷺ)

كُلّ مُسكِرٍ حَرَامٌ

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ROLE OF THE MOSQUE IN CONFRONTING THE EPIDEMIC OF SUBSTANCE ABUSE

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This article will throw light on the experiment conducted by Prophet Mohamed (ﷺ) in the early days of Islam to curb the epidemic of alcoholism making use of the mosque as a center of his campaign. The success he gained in minimizing the acceptance and abuse of alcohol up to the present time was and still is a model that can be adopted successfully.

The article will shed light on the experiments conducted in Egypt nowadays to make use of the mosque as a center for prevention and treatment of this epidemic giving facts and figures as well as the difficulties confronted and how they were overcome.

The Islamic Plan To Combat Alcoholism

It is well known that alcoholism was wide spread all over the Arab Peninsula. The acceptance of the people for alcohol use was at its acme. Literature specially poetry reflects this fact. The deliterious effects of alcoholism was manifested on the social life conducting the tribes to continuous conflicts and wars.

The main approach to the problem by Islam, was to adopt gradation in forbidding alcoholism. This was carried out side by side with improving the social conditions of the people. Faith played a major part in these two approaches. The time estimated from the beginning of the campaign to its end was about 15 years. The personality of the leader, "The Prophet" (ﷺ) was revolutionary affecting this change. The model he (ﷺ) gave as a 1st step was the true example adopted by him and all his near followers and so they were respected and their pieces of advice were accepted, absorbed, well learned and maintained denoting absolute response:

> *"THE PROPHET GAVE TRUE EXAMPLE TO BE FOLLOWED"*
>
> *(S.33:V.21)*

The 2nd step was disseminating knowledge about the evils of alcohol that it is deliterious and detrimental:

> *THE BELIEVERS ENQUIRE ABOUT SPIRITS AND GAMBLING. INFORM THEM THAT THEY HAVE THEIR EVILS AND USES FOR PEOPLE BUT THEIR EVILS OUTWEIGH THEIR USES*
>
> *(S2:V.219).*

Thus drawing the attention to the deliterious effects of using spirits and gambling. The 3rd step was rather decisive, it says blankly.

> *YOU BELIEVERS DO NOT APPROACH PRAYING WHILE YOU ARE UNDER THE EFFECT OF ALCOHOL.*
>
> *(S.4:V.43)*

Thus minimizing the abuse during most of the day, as the five prayers extend from dawn time until night fall. The 4th step came when the people had matured enough to accept it through the penetrating model, the persuading orientation and the partial legislation. It was related that one of believers namely "Omar Ebn El Khtab" said in a meeting in the mosque "Oh Allah give us a decisive say about alcohol". At this time of real faith and maturation the last step was declared by the verse saying:

YOU BELIEVERS, SPIRITS, GAMBLING, IDOLS AND FORTUNE TELLING ARE ALL EVILS WHICH YOU SHOULD ABANDON THAT YOU MAY PROSPER

(S.5:V.90)

These vital steady steps treating the social and the spiritual side were the two pillars upon which the plan of combat rested.

History states that since the last verse the majority of the abusers abstained and the people lived without alcohol and did not drink or touch or sell or buy or sit with abusers or even carry it. This picture is unique in history and is a witness of the sucess of the campaign. From the above stated example we can deduce the items of the Islamic approach.

1. The model of the leader.
2. The dissemination of information about the evils of abuse.
3. Legislative steps were gradual hand in hand with these approaches and the change was to the better of the social life of the people.
4. The law of prohibition and imposing punishment for abusers came last.

In this respect I would like to refer to the Chinese plan of combating opuim abuse in this century which followed more or less the same procedure leading to success. The U.S.A. attempt to combat alcoholism by an abrupt law, led to aggravation of the situation.

Spot Lights on the Experiments Conducted in Egypt About the Role of the Mosque To Combat Drug Abuse

1. Since 1968 a clergyman was appointed to work with the therapeutic team in treating drug abuse. This was conducted in Ataba Clinic in Cairo. This approach led to a quick increase of the number of admissions to the clinic:

1968	104
1969	405
1970	1409

   It also led to the success of the group therapy sessions.
2. W.H.O. has been briefed of the new approach which was evaluated and its validity was endorsed.
3. A clinic was annexed to Abou El Azayem mosque which lies in a congested area. The policy of the treatment was to make use of the psycho-socio-religious-dynamics. The preachers selected were trained and given adequate information about the plan of treatment.

Analysis of the Content of the Speeches of the Preachers

When the content of their speeches were analysed, it was found out that, they were not well oriented about

(1) The psychological or the social approach to the problem.

(2) The real state of the picture of addiction and the diverse types of dependence.

(3) The effects of dependence physically, psychologically and socially on the patient.

(4) How to make use of persuation and suggestion in an individual or group session.

Refer to the report on comparative evaluation of the voluntary treatment of opium dependents Project 03-275-A. ADAMH. 1985.

Training of the Preachers

It is worth mentioning that the results of interviewing these preachers revealed the fact that some had the same false views and misunderstanding common in the community about the causations lying behind neurotic and mental diseases as well as drug addiction in particular. Thus the training was based on scientific facts to change the concepts and attitudes of the preachers inorder to communicate these facts to the community through their activities in the mosque.

Training of The Preacher Amongst The Therapeutic Team

The training was conducted on a full time scale at Dr. Abou El Azayem Hospital. W.H.O. participated in the program.

This training was a new approach in a new area of activity using the preacher in the therapeutic team. Some psychiatrists did not approve of this new step and did not show enough cooperation in this respect and so it was a burden on the organizing bodies to overcome this gap. Some preachers were not convinced and attributed addiction for example to the effect of devilish curses or other unseen powers and thus it was necessary to change their fixed ideas by coexistence training amongst the patients themselves to gain a 1st hand experience.

Others were only keen to point out the blazing hell awaiting the abusers. These were contented by pointing out the religious code connected with dependence rather than to penetrate into the depths of the problem to help the abuser to change the attitude and abstain by the power of faith and self persuation.

Those who succeeded in their mission were those who respected the other members of the therapeutic team and cooperated with them in a friendly way towards the same goal, trying to vaccinate and inoculate faith in the treating doctor and faith in the social work side and in the same time potentiate the will power and patience of the abusers giving the sublime meaning connected with the effects of faith and patience on the secretion of hormones from the C.N.S., a mechanism which is endowed to everyone who keeps to the right path and an ability to bear the pains of abstaining.

Prayers as a Therapeutic Tool

The policy of the daily program of these clinics depended on observing the prayers at their declared time in a group of all those working in the clinic and the patients participated and all led by the preacher who invited them all after the end of the prayer to the group therapy religious sessions in which all the members of the team cooperated.

In these open sessions the therapeutic team, which has been well trained in using faith as an article for therapy, participated and answered questions trying to explain the merits of the religious orders, the real meaning of cleanliness, ablution and its effect on the central nervous system; the effect of group prayers psychologically and their tranquilising effect.

These sessions widened the sphere of interest of the participants in their daily program and how to make use of their time pleasurable, constructive and recreational.

This training constituted the corner stone on which the role of the mosque was erected.

Evaluation of the Role of the Mosque

When the clinical results of the experiments were declared, the WHO asked for evaluation and suggested to approach the National Institute of Drug Abuse in Washington.

A protocol of research was prepared to evaluate two clinics, one an office clinic and the other a clinic annexed to a mosque where psycho-socio-religious approaches are used.

Ataba clinic in the center of Cairo was the office clinic. Abou El Azayem clinic annexed to the mosque was the second. A double blind experiment was conducted where 4 different modalities were used in the treatment of 4 groups of male opium dependents living in the center of Cairo. The 4 groups in the office clinic (Ataba) were compared to 4 groups in the mosque clinic (Abou El Azayem). Each group of patients was comprised of about 40 cases. The 4 different modalities were:

(1) Treatment with antidepressant drugs.
(2) Treatment with insulin modified.
(3) Treatment with antidepressant drugs and insulin.
(4) Treatment with placebo.

The outcome data of the treatment after about one year treatment and follow up were computerized and the results were recorded.

After deciphering the outcomes, the following was found.

The patients who resorted to the mosque clinic were those who were more involved in the drug abuse and were of the chronic cases who relapsed several times. Following are some initial differences.

(1) 11.50% of Ataba volunteers vs. 21.25% of mosque patients spent E.L. 4 or more daily on drugs.
(2) 9.41% of Ataba people vs. 15% of mosque patients reported taking the drug 3 or more times daily.
(3) 57.55% of those treated at Ataba vs. 70% of those at mosque reported becoming "nervy" when not taking the drug.
(4) 29.71% of Ataba takers vs. 47.50% of mosque users reported being unable to bear withdrawal symptoms (therefore resuming drug consumption) after a period of sobriety.
(5) 5.8% of Atab Ss vs. 10% of mosque Ss stated that they spent their leisure time at Cafes.
(6) 58% of Ataba patients vs. 13.75% of mosque Ss maintained that both their financial and health conditions urged them to seek treatment of drug dependence.

In their totality it is clear that the serious cases went to the mosque clinic, this denotes increase faith of the community towards the religious organization. This faith is thus a potent weapon in the combat campaign.

After thorough analysis of the withdrawal symptoms and the relief of these symptoms by the different treatment modalities the experiment declared that the Mosque clinic gained 7 score while the office clinic gained only 3 denoting a notable success in the mosque clinic.

It was also recorded that the outcomes of the placebo modality, where the cases were injected with aqua (water) and given a capsule of starch (inert substance) was to the same effect as the treatment with antidepressants and also insulin treatment.

This fact needs a stand and analysis specially that the cases who were under placebo in the mosque clinic addicted to the injections and the capsules.

They asked urgently to have this treatment when we stopped the experiment. When they were asked about its effect they stated that the treatment potentiated their abilities and gave them peace of mind and

tranquilization.

This fact reveals the role of faith in the treatment. It also reflects light on the effect of patience and the role of endorphin in relieving pain and stabilizing the cases.

This is a proof of the importance of faith and it throws light on what can be achieved from the community mental health mosque.

In Egypt there are about 75000 mosques. Out of these mosques, about 1000 mosques, a community mosque where different social, educational, therapeutic and rehabilitative activities are conducted.

The move is going on though slowly to involve these mosques in the campaign.

It is recommended that:

1. Extensive training should planned for the preachers to cope with that movement.
2. A central organization should be formed to plan, take care of, follow up, initiate other organizations and mosques to follow suit, and to help in convening conferences and congresses about the role of the mosque in mental health generally and combat of drug addiction specially.

Important Statistical Data Which Should Be Taken Into Consideration in Planning for A Therapeutic Policy

- ⋆ It has been manifested that there are waves of increase in voluntary admission to clinics seeking treatment. This coincided with the increase of the price of the drugs in the underground market. This increase of the price is usually due to active successful police campaigns.
- ⋆ Statistical language says that when the police took active measures against the addicts themselves, the dependents refrained from looking for treatment, for fear of being detected. This means that applying the step by step approach paves the way for increasing the will power seeking for treatment.
- ⋆ There is also an increase in voluntary admission for treatment as a result of active mass media against dependence. This means there is a need for increased orientation on all levels.
- ⋆ It has been also manifested that opening clinics near or amidst the infected areas increases the move towards the seek for treatment. This means that the clinic attached to the mosques are the most appropriate places for the campaign.
- ⋆ It is clear that the non-governmental associations took the initiative to tackle the problem, so we should plan to activate these non-governmental bodies to potentiate their work and to co-operate together for more productive efforts.

A Call For An Urgent Legislative Step

After all the above stated facts which are the outcome of extensive research in this field it is expected that the authorities should take a legislative step to formulate the necessary articles of a manifest to combat drug dependence.

The Suggestive Articles Are

1. A plan of five years should be drawn to
    1. Open clinics in the religious centers or Mosques and churches.
    2. Train personnel needed for the campaign with special emphasis on preachers.

3. Activate mass media on all levels.
4. Potentiate police campaign.
5. Fix a time limit to give up dealing in or handling or trafficking or using any form of drugs and thus it will be clear that abusers will be liable to punishment if they do not observe the law.

This time limit should be respected and observed by the community and the authorities.

2. Execution should be the penalty for the traffickers or dealers openly and quickly.

CHANGING PATTERN OF DRUG ADDICTION

Prof. Dr. Mahmoud Sami Abdel Gawad

EYPT

ABSTRACT

Addiction is a multiphasic problem which results from interaction between many factors. This retrospective study was conducted in one of the private psychiatric hospitals in Cairo by studying the files of addicts registered in the period from 1972 to 1986. Their number was 461. The following results were observed:

1. There was marked increase in number of addicts in recent years (1982-1986).
2. The increase in number of addicts abusing new types of opioids as heroin was highly significant as they represented 0% in the period from 1972 to 1976 and 57.36% in the period from 1982 to 1986.
3. The marked increase in heroin addiction was interpreted in terms of availability, having potent, rapid and dramatic action.
4. The economic changes affecting the Egyptian Culture in recent years participated in the changing pattern of addiction.

Bulletin of Islamic Medicine, 5: (65-87), 1988.

CAUSES OF RECIDIVISM IN NARCOTICS CRIMES

Captain Hamad Abdulla Al-Srayea
KUWAIT

INTRODUCTION BY THE RESEARCH AND STUDIES DEPARTMENT

This study is by all means not the first nor the last in this area. It is just a continuation to other studies performed regarding the narcotics problems, in an attempt to shed some light on the social, economical and legal reasons which lead to recidivism to narcotics crimes.

The widespread of the recidivism phenomenon in narctics related crimes was the motivation for this research project. Reasons of recidivism are sought in addition to the status of the recidivist.

The implementation of this research project comes at a crucial time for Kuwait and neighbouring countries. They all need to foster their effort to combat the narcotics waves of crime. The recidivism is one aspect of it and this project outlines the reasons for this phenomenon.

The importance of this project lies in the opportunity to make use of the existing data and information in order to limit or combat the phenomenon of recidivism. In addition to that, the research presents definite guideline to the decision makers concerning the range of recidivism in narcotics crimes. The social, economic and legal aspects of the phenomenon are detailed and dealt with subjectively. We hope that the results and recommendations shall be of use to all concerned for the prosperity and safety of our country.

Director of Research and Studies Department
Colonel Abdul Majeed Ibrahim Khoraibet

INTRODUCTION BY THE GENERAL DEPARTMENT OF CRIMINAL INVESTIGATIONS

Research Concept

Narcotics abuse has become a worrying problem worldwide, without any exception, whether a country is a producer, a transit point or a consumer. The sincere international co-operation is a necessity for the efforts to combat narcotics abuse. This problem is a major cause for the destruction of youthful capabilities and its annual death related figures have sky-rocketed in recent years. This spurred efforts to boost the narcotics combat agencies. An important part of such efforts is to cater for persons apprehended for narcotics abuse and to investigate their social, economic and legal affairs. The continuous increase in the number of offenders creates a major burden on all instruments dealing with narcotics abuse.

The role of the combat agencies could be further strengthened if their efforts were concentrated in fighting international smuggling and local dealers, with the assistance of other related agencies to provide parrol

reports about ex-convicts and probable second offenders or recidivists. Other agencies should, also, be asked to take care of the social, economic and legal aspects of the narcotics abuse phenomenon.

REASONS OF RECIDIVISM IN NARCOTICS CRIMES

Research Objectives

The main objective of the research is to determine and analyze the major social, economic and legal causes which led to drug abuse crimes for Kuwaiti inmates at the Central Prison which reverted to crime more than once. In addition to that, the research sheds light on certain personal characteristics and details of the inmates and its relation to recidivism.

Research Procedure

The research population has been selected from Kuwaiti inmates at the Central Prison detained for drug abuse crimes more than once. The descriptive survey and data collection has been accomplished through a questionnaire specifically prepared for this study. The questionnaire contained 27 questions, which are grouped into five sections: (1) demographic data, (2) particular detail, (3) social causes, (4) economical causes and (5) legal causes.

The questionnaire form reached 27 inmates, that is 54 percent of the total inmates (50 detainees).

Ratios and number of repetitions have been used in the analysis of the data.

Research Results

(1) Most of the recidivists in narcotics abuse crimes were males between 26-35 years of age, socially stable. Their educational level between elementary and intermediate school, employed in the public sector and their average monthly income ranged between 300 - 400 Kuwaiti Dinars.

(2) Most of the recidivists in narcotics crimes were for abuse and dealing charges sentenced between 2-10 years imprisonment.

(3) The social factors which led most recidivists to crime were: spoiling, marital differences and the like, bad company and other occupation related factors.

(4) The economic causes were confined to availability of money, job stability and plenty of leisure time.

(5) There were no legal causes for recidivism. There was a general feeling of discontent to certain articles of the law, particularly the inconsistency between charge and sentence, or that the final investigations were not fair.

CHAPTER ONE
PROBLEM DEFINITION

INTRODUCTION

This chapter contains subjects related to the definition of the narcotics recidivism problem. It covers the background of the problem, the importance of the study, purpose of the study, questions answered by the study, study limits, terminology, summary and organization.

BACKGROUND

The main objective of setting up the narcotics and alcohol combat department in Kuwait is to limit and lessen the extent of drug spread in general, and to find means to control the recidivism to such crimes. To this end, the department of narcotics control have deployed and shall continue to deploy all available material, moral and human resources, and in addition to that the department expects from others concerned in narcotics abuse, to continue planning for means to block the way for recidivists to go back into narcotics crimes. By the same agrument, others concerned in narcotics abuse expect the department to respond to their needs towards fulfilling the same objective. For certain reasons, unknown to us, some individuals went quite far in their indulgence into narcotics abuse crimes. This behaviour have been noticed by official responsible for combating drugs in Kuwait. It is beyond doubt that openers of Kuwait towards the outside world have played a considerable role in encouraging drug offender for a second offence or even several offences, recidivism.

THE PROBLEM

The main objective of this research project is to obtain knowledge concerning the cuases of recidivism in narcotics abuse crimes, in Kuwait, from social, economic and legal aspects.

Therefore, the problem shall be investigated within such aspects.

IMPORTANCE OF THE STUDY

As has been discussed earlier, the research has focused on three aspects related to recidivism in narcotics crimes, many other aspects were not included at this stage. The researcher considered that social, economic and legal aspects are the most relevant and important for his ends. The importance of the study lies in the extent of application and use of obtained information, in order to help drug combat agencies in their continuous quest to develop its forces against the increasing problem of drug abuse. Also, the information obtained shall be useful in pinpointing the requirements of drug combat agencies in order to make a better job of their work.

All organizations concerned with drug abuse shall, undoubtedly, benefit from the wealth of information obtained about means and activities leading to recidivism. Such information shall be pooled and augmented with existing knowledge for increased efficiency in combating drug abuse. This research project shall put the narcotics combat officials into perspective regarding the extent of the recidivism phenomenon. A better appraisal for the needs and requirements of security men working in drug control shall be developed. Recommendations for better facilities will fall on a better responsive ear. Also a better coordination of efforts is anticipated. Drug control organizations shall concentrate on its role to limit the spread of drug abuse, and other organizations shall be responsible for keeping an eye on probable recidivists.

The study shall give further benefits in the following areas:

1) Increase in the number of qualified and trained personnel in drug abuse combat to balance the ever increasing number of offenders.

2) Paying attention to the social conditions for persons detained for drug abuse cases, and finding means for their normal re-introduction into the society.

3) Creating an interest in the economical situations of people arrested for drug abuse charges, and assisting them to find legitimate sources of income in order to support their families.

4) Giving consideration to the legal aspects of narcotics problems, and creating trained efficient staff in both public attorney and juidicial chords.

5) Giving consideration for setting up specialized courts for drug abuse cases, similar to juvenile courts.

PURPOSE OF THE STUDY

The basic purpose of this study is to determine and analyze the most important social, economic and legal causes related to recidivism in drug abuse crimes, hoping that such determination and analysis shall assist relevant officials to:

1) Appraise the extent of the problem socially, economically and legally.

2) Drawing up a planning policy for training the required staff in order to combat such problem.

3) Evaluation of existing programs designed for limiting the problems of recidivism in narcotics cases.

4) Specifying the requirements of security personnel and narcotics combat department.

5) Determining the social, economic and legal causes of recidivism in narcotics cases.

QUESTIONS ANSWERED BY THE STUDY

As previously mentioned under the heading "purpose of the study", the questions that this project will attempt to answer can be phrased as follows:

1) What are the available personal and technical informations concerning recidivists in drug abuse crimes?

Relevant questions to this effect have been included in the study questionnaire. Indicators from such characteristics and details were sought in order to indentify probable second offenders or recidivists. In other words, are recidivists different in their personal details from others? The question shall be answered by analyzing data obtained from the questionnaire.

2) What are the social, economic and legal causes that might lead to recidivism?

Multiple choice answers where furnished for the subjects in order to indentify the suitable causes for each case. The causes were concerned with the aspects mentioned.

STUDY LIMIT

The study has been confined to include Kuwaiti recidivists only, either detained pending a narcotics case or have already been convicted, sentenced and present at the Central Prison in Sulaibikhat. Therefore, the results of this research shall only apply to a similar set of conditions.

The study excluded other inmates and recidivists females. It should be noted that the study did not include non-Kuwaitis since expatriates are deported after serving their sentence. Thus there are no non-Kuwaitis recidivist.

TERMINOLOGY

Recidivist: a person who has recurred to committing a crime related to narcotics such as dealing, abuse, trafficking or transporting.

Detainee: a person confined in the prison pending investigations.

Convict: a person serving time in prison after being convicted and sentenced.

Narcotics: a set of materials and drugs causing harm to the health of the human if abused. Narcotics have been defined by Al Mughrabi as "every raw material or product containing an asthetic or awakening essence which if not used in determined medical or industrial purposes, shall be psychologically and socially harmful to the individual and society"[1].

SUMMARY OF THE FIRST CHAPTER

The first chapter contained subject related to the definitive aspect of the problem such as: background, the problem, the importance of the study, the purpose of the study, questions answered by the research, the limits of the research and definition of terminology employed.

ORGANIZATION

The second chapter relates to previous studies either in Arabic or Foreign languages. Chapter three is concerned with the methodology of the research, including selecting the sample and subjects, data collection, validity of collected information, data analysis and the questions of the research.

The fourth chapter presents the results, data analysis and answers to the questions of the study. The fifth and final chapter contains summary, conclusions and recommendations of the project.

CHAPTER TWO
PREVIOUS STUDIES

ARABIC STUDIES

The drug abuse problem and its related aspects such as dealing, addiction or even medical abuse has turned into an international dilema. Kuwait, due to its geographical position and the high numbers of expatriate from diversified countries, has not been able to avoid being part of the worldwide concern for drugs and narcotics abuse. Many expatriates brought to Kuwait their different customs and traditions. It could be considered natural for Chinese, Korea or Thai to take drugs, but such practice, stricts against local Islamic and Arabic tradition in Kuwait. As Colonel Abdullah Saeed Al Farhan[2] mentioned in his book titled "Kuwait and the International Efforts for Drug Combat, 1985" the narcotics problem in many countries are quite national problems whereas in Kuwait it is not that serious. This is not an under estimation but rather a statistical fact, since statistics indicate that the problem is confined to a narrow range of categories of expatriates and a slight percentage of Kuwaitis".

Gulf States in general, and Kuwait in particular can be considered as a transit point for most other countries, geographically speaking. This also applies to the most parts of east Asia and the far east. This encourages certain groups of the people of these countries to indulge in drug and alcohol dealing. In a research prepared by General Yousef Gharabieh[3] under the title "Narcotics Problems in the Arab Region, 1984", mentioned that "narcotic problems have international characteristics. This was helped by the ease of transportation and promptness of communications and the integration of all countries in the globe. Narcotics and other materials have an easier job nowadays to pollute the whole world".

A major consideration in this context is that the Gulf area has wealth of jobs and plenty of opportunities with high returns and no taxes. This is definitely quite an attraction for labour force from east Asia and the far east. The labour force brought to the area non-Arabic customs and traditions which mixed with the Arabic customs and traditions. Such a mix or integration was in certain cases accompanied by a kind of rejection which was manifested in socially unacceptable behaviour. For example, freedom to take decisions, rejection of family traditions.

In this context, Dr. Abdul Rahman Al Musaiger[4] in his research about "Youth and Narcotics" mentioned that "The importing of labour force is one of the most important political, economical and demographic phenomena that have been witnessed in Arab Gulf states during the last decade. The job opportunities created by the petroleum income caused a massive influx of foreign labour force, especially from Asia. This in turn caused a deviation in the demographic composition in these states which has reflected on the social conditions in the Gulf States. The incoming labourers brought with them their behavioral deviations which are markedly different from their couterpart in the area".

As a result of this population intrusion and the wish of the expatriates to express their needs and requirements, an atmosphere of uncompatibility was created between the imported customs and the traditions of the host countries. In order to deal with these challenges, the drug combat department have deployed all necessary capabilities and resources to limit or decrease the spread and distribution of drugs in Kuwait. It intensified the co-operation with customs and ports officials locally and with drug combat officials in Gulf Co-operation Council Countries and with relevant international organization and agencies.

FOREIGN STUDIES

A great deal of scientific literature is also available on the subject of habitual narcotics crimes. A British researcher (Engel)[5] investigated the use of rehabilitation to cure persons of recidivism record. By use of a case study, he managed to convince the individual that he can do major contributions to his society and rid of the aggressive behaviour. This particular study went further than exposing the recidivism phenomena to the normal return into the society.

In Poland, Poznaniak[6] examined the trends of criminals and non-criminals towards ethical values in the society, using an equally divided sample of 100 persons. The study showed that recidivists have negative indicators for all moral values, and that they believed that such values are not observed by the society, therefore they are fake. The most negative attitudes were against law enforcement agencies where they considered personnel in these agencies unethical compared to themselves. This clearly indicates the importance of the type of treatment the convicts receive in recidivism.

An American researcher (Asch)[7] noticed during study of the ego and superego in recidivists that such people have special deviation in both the ego and superego. Also, he measured and evaluated the effectiveness of punishment against such persons to suit the kind of ego and superego for recidivists.

It should be noted that so many studies have been completed in relation to narcotics crime from health and psychological stand points. This particular study is rather different since it investigates the social, economical and legal causes of recidivism.

CHAPTER THREE
METHODOLOGY

INTRODUCTION

The basic purpose of this study is to determine and analyze the different kinds of causes whether social, economical or legal, that prompted perpetrators to return to narcotic crimes. Having this purpose in mind, the study methodology has been designed in the following fashion: sample and subject identification, data collection (including preparing the questionnaire, questionnaire validity and collection techniques), statistical analysis of the three segments of the questionnaire, the basic theory of descriptive statistics employed, the research assumptions and questions, and finally the summary.

SAMPLE AND SUBJECT IDENTIFICATION

The total sample of the research was Kuwaiti males convicted or detained due to returning to a narcotics crime, present at the Central Prison in Kuwait in 1988. It was expected that fifty male prisons would participate, the number of female inmates was quite small. Out of this expected total, the researcher managed to reach only 27. Others either have rejected to participate or have not been reached. The quantitive analysis is, therefore, relevant to 27 inmates only.

DATA COLLECTION

DESIGN OF THE QUESTIONNAIRE

The researcher decided to design his own data collection tool (a questionnaire) due to the lack of a pre-prepared form and the need to explain some of the terminology used in the study. Extensive reference was made to locally designed questionnaires and continuous contact was maintained with sociologists and magistrates. The questionnaire, titled "Causes of Recidivism in Narcotics Crimes", is composed of five sections: demographic data, technical particulates, social causes, economic causes and legal causes.

SECTION 1 - DEMOGRAPHIC DATA

This section has been formed in order to obtain some of the personal information which may be linked to or associated with recidivism in narcotics crimes. This section shall be used to perform the age distribution of the sample, social status distribution, number of wives, educational status, employment status and monthly income (see Appendix B).

SECTION 2 - TECHNICAL PARTICULATE

This section serves to obtain information relating to the way that led to recidivism in narcotics crimes, such as number of arrests, type of the first charge, and subsequent charges, the current detention status and the sentence passed against him. (Appendix B).

SECTION 3 - SOCIAL CAUSES

This section is formed in order to get certain social causes that prompted perpetrators to return to crimes in narcotics. The subjects were requested to mark the correct choices for their marital status, close friends, and the effect of employment conditions on recidivism in narcotics (Appendix B).

SECTION 4 - ECONOMICAL CAUSES

This section is relevant to economical causes of recidivism such as availability of money and income, employment condition, the desire for immediate wealth and the desire for a leading economical status amongst friends (Appendix B).

SECTION 5 - LEGAL CAUSES

This section tries to outline some negative aspects of the law, its application, or its suitability to the conditions and factors in the region. The section searches for legal flaws or loop holes, poor deterent first sentences, or further sentences, poor preliminary or final investigation procedures, insuitability of punishment period in relation to the crime, lowering the age limit for imprisonment and other causes (Appendix B).

VALIDITY OF THE QUESTIONNAIRE

The questionnaire was reviewed by a group of specialists in psychology and sociology in order to establish the validity of the data to be collected. The questionnaire was later revised to reflect their comments. Appendix C presents a copy of the letter that was sent to the designated specialists. A pilot survey was not possible for further validation by the inmates.

COLLECTION PROCEDURE

The questionnaire was distributed on Saturday 7th of May 1988 to a group of recidivists of narcotics crimes at the Central Prison in Sulaibikhat. The prisoners were brought in groups ranging from 5 to 10. Twenty seven out of fifty inmates were interviewed. The others were considered out of the project.

DATA ANALYSIS
STATISTICAL ANALYSIS

Descriptive analysis was employed in the data analysis to determine the number of repetitions and their percentages. The data was tabulated in a suitable form to reflect the social, economic and legal causes of recidivism.

THEORETICAL BASE FOR DESCRIPTIVE ANALYSIS

The analysis was confined to descriptive statistics due to the size of the sample. It is used in such circumstances to determine the number of repitition and percentages for each response. This kind of analysis is characterized by summarizing the data in easily descriptive tables.

RESPONSE

Fifty inmates of recidivism record in narcotics crimes were selected as total sample for this study. It managed only to reach 27 of them (54%).

RESEARCH QUESTIONS
SECTION 1 - DEMOGRAPHIC DATA

The section of the questionnaire contained some particulars about the inmate such as the number of arrests, the charge at each arrest, the existing condition of detention and sentence passed against him. The qualitative description was used to provide answers for the following questions:

1. What are the available personal and technical information about recidivists in narcotic crimes?

2. What are the social, economical and legal causes for recidivism in narcotic crimes?

The first question was answered in the first and second sections, the second question in the third, fourth and fifth sections.

A detailed description follows for each of the questions.

To answer the first question, the inmates were given a set of personal and technical questions and they were requested to tick the correct data. The purpose of the question is to determine and analyze the personal and technical characteristics. Also, to establish if the changes to personal and technical details might be a factor assisting in recidivism.

THIRD, FOURTH AND FIFTH SECTIONS - SOCIAL, ECONOMIC AND LEGAL CAUSES

These sections of the questionnaire contained information pertaining to the social, economic and legal causes. As a part of social conditions, the following were included: the status of the perpetrator amongst his family, marital relations, doubts about the wife, lack of suitable atmosphere in the house, encouragement from the wife, friends and work mates. The economical causes include: income and availability of cash, employment conditions, greediness, the desire for immediate wealth and leading economical position amongst friends.

The legal causes included: negative aspects of the law or of applying the law, the suitability of the law to the conditions in the region, existence of loop hole, or gaps, weakness of sentences in the first degree or in appeal, weakness of final investigation at court, unsuitability of crime to punishment and reduction of imprisonment sentences. The qualitative analysis was then used to provide an answer for the second question: What are the social, economic and legal causes of recidivism in narcotics crimes?

The inmates were presented with a set of questions that reflect the most important social, economic and legal causes. Each inmate was asked to tick the reason that caused his return to committing narcotics crimes.

RESEARCH POSTULATES

It is assumed that if the social, economic and legal causes of recidivism and the accompanied personal and characteristics details have been defined and analyzed, the officials concerned with combating drugs shall have a better understanding of the problem. They shall be better equipped to handle it and have a wider vision of the events and the extent of its effects. This shall, definitely, put them closer to fullfilment of their objectives.

It is further assumed that if the requirements of the drug combat agencies are met, then the objectives of the department shall be best achieved.

The other assumptions of the study are:

1. The number of recidivists is steadily increasing.
2. The number of combat staff does not balance the increasing number of recidivists, in narcotic crimes.
3. The threat of drug dealing is mounting due to the location of Kuwait between producing countries and consuming countries.
4. The recidivism in narcotic crimes has grown to be a noticeable phenomenon.
5. The Narcotic Combat Department exerts continuing efforts to limit and reduce the widespread of drugs and recurrence of drugs crimes.
6. The determination and analysis of habitual narcotics crimes shall assist in determining the requirements and needs of combat and investigation authorities.

SUMMARY OF THE THIRD CHAPTER

The third chapter included subjects related to sample and subject definition, data collection techniques including questionnaire composition, validity and compilation, the analysis of data collected in the three segments of the questionnaire, the type of statistical analysis employed, the theoretical basis for qualitative analysis, extent of response to the questionnaire, research postulates and answers to the research questions.

CHAPTER FOUR
RESULTS

INTRODUCTION

The chapter contains intensive analysis of the collected data. The analysis included the results of the first section concerning demographic data, the second section containing technical details about the recidivists, the third section about the social causes, the fourth section about the economical causes and the fifth section about legal causes leading perpetrators back into narcotic crimes. The results are summarized in simple terms at the end of the chapter.

RESULTS OF DATA ANALYSIS

The review of records at the Central Prison revealed that there were fifty inmates who qualify as recidivists in narcotic crimes. The study questionnaire managed to reach 27 of them (percent), the others were unavailable at the time of application of the questionnaire.

ANSWERS TO RESEARCH QUESTIONS

SECTION 1 - DEMOGRAPHIC DATA

The first of the questionnaire requested the inamtes to provide certain personal details, that could be used to explain recidivisim. This assumes that the social condition (number of wives, educational level, occupational level, level of income, etc) is somewhat related to recidivism.

This section of the questionnaire was designed to give an answer to the following question:

What are the available personal information about recidivists in narcotic crimes?

AGE

Table 1 presents the age distribution of the subjects. It demonstrates that the majority of recidivists in narcotic crimes are between 31-35 years old. They comprise 40.7% of the total respondents. Next comes the 26-30 age group, 25.9%.

TABLE 1: AGE DISTRIBUTION OF NARCOTIC RECIDIVISTS

Age Group	Number	Percentage %
18-21	—	—
22-25	1	3.7
26-30	7	25.9
31-35	11	40.7
36-40	5	18.5
Over 40	3	11.1
Total	27	100%

SOCIAL STATUS AND NUMBER OF WIVES

Table 2 gives the social condition and number of wives for subjects. It is clear that married subjects out-number unmarried. 15 inmates (55.6%) are married, only one had more than one wife.

TABLE 2: MARITAL STATUS AND NUMBER OF WIVES FOR NARCOTIC RECIDIVISTS

	Number	Percentage
Married - one wife	15	55.6
Married - more than one wife	1	3.7
Three Wives or more	—	—
Single	9	33.3
Divorced	3	11.1
Widower	—	—

EDUCATIONAL LEVEL

As shown in Table 3, most narcotics recidivists were of preliminary or intermediate school level, 70.4% percent, while those who completed secondary education level were 22.2% of the total subjects.

TABLE 3: EDUCATIONAL LEVEL FOR NARCOTICS RECIDIVISTS

Educational level	Number	Percentage
Illiterate	2	7.4
Read & Write only	—	—
Preliminary/Intermediate	19	70.4
Secondary	6	22.2
University graduate	—	—

EMPLOYMENT CONDITION

Table 4 presents the employment conditions for narcotics recidivists. 13 out of the 27 respondents to the questionnaire (48.1%) were employed by the public sector, while 5 (18.5%) were unemployed at the time of arrest.

TABLE 4: EMPLOYMENT LEVEL FOR NARCOTICS RECIDIVISTS

Employment Conditions	Number	Percentage
Public Sector Employee	13	48.1
Private Sector Employee	3	11.1
Private Business	6	27.2
Unemployed	5	18.5
Other categories	—	—
Total	27	100%

LEVEL OF INCOME

It can be inferred from Table 5 that the income level of KD. 300-400 was the most common (8 inmates) 29.6%, next comes the group KD. 100-200 (4 inmates) 14.8%.

TABLE 5: LEVEL OF INCOME FOR NARCOTICS RECIDIVIST

Income Group KD.	Number	Percentage
100 - 200	4	14.8
201 - 300	2	7.4
301 - 400	8	29.6
401 - 500	2	7.4
501 - 600	3	11.4
Over 601	3	11.4
Total	22	81.4 %

SECTION 2 - TECHNICAL DETAILS

This section of the questionnaire requested the inmates to provide certain technical details related to their apprehension. The section was designed to answer the following question:

What are the technical details available concerning recidivists in narcotic crimes?

NUMBER OF ARRESTS FOR A NARCOTICS CHARGE

Table 6 shows the respective number of arrests for narcotic recidivists. Sixteen (59.2%) of the inmates had two arrests, 7 (25.9%) were arrested three times.

TABLE 6: NUMBER OF ARRESTS FOR NARCOTICS CHARGES

Number of arrests	Number	Percentage
Two times	16	59.2
Three times	7	25.9
More than three times	3	11.1
Total	26	96.2

THE CHARGE AT EACH ARREST

The introduction regarding the charge at each time of the respondent's arrest is presented in Table 7. It can be easily noticed that first and second arrests for drug abuse or dealing are far greater than those for middleman.

TABLE 7: THE CHARGE AT EACH ARREST FOR NARCOTICS RECIDIVISTS

Number of charges	First Time		Second Time		Third Time		Over Three Times	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Abuse	14	(51.9)	13	(48.1)	3	(11.1)	2	(7.4)
Fetching	2	(7.4)	1	(3.7)	1	(3.7)	—	—
Dealing	9	(33.3)	6	(22.2)	6	(22.2)	1	(3.7)
Middleman	1	(3.7)	—	—	—	—	—	—
Total	26	(96.3)	20	(74)	10	(37)	3	(11.1)

EXISTING STATUS OF DETENTION

It has been found that 78% of recidivists in narcotics crimes have been sentenced to a period ranging between 6 month to 10 years. Table 8 presents the existing status of detention for the subject inmates.

TABLE 8: EXISTING STATUS OF DETENTION FOR SUBJECT INMATES

Status	Number	Percentage
Detained pending trial	6	22.2
Sentenced	21	77.8
Total	27	100%

NUMBER OF DEFENDANTS

At this point it should be emphasized that the number of narcotics offences is steadily increasing, and especially recidivists. The following statistics give us clear indications to such increase from 1978 to 1987.

Crime Type	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987
Producing narcotics for dealing purposes	—	—	—	—	—	—	—	1	1	1
Possession of narcotics for dealing purposes	12	17	15	18	30	30	40	42	49	49
Selling narcotics for dealing purposes	32	39	38	48	96	73	73	83	92	111
Spread of narcotics for use purposes	4	5	7	9	9	19	16	16	15	15
Fetching narcotics for use purposes	—	—	—	—	—	—	2	2	3	1
Possession of narcotics for personal use	12	13	16	20	21	28	39	39	50	52
Fetching drug for plantations for personal use	—	—	—	—	—	—	—	—	—	1
Total	60	70	76	95	116	150	170	183	210	230

RESULTS OF THE THIRD, FOURTH AND FIFTH SECTIONS

SOCIAL, ECONOMIC AND LEGAL CAUSES

The inmates were requested in these sections to provide answers and information regarding the most important social, economic and legal causes that encourage the perpetrator to return to narcotics crimes. The sections were designed to give an answer to the following question.

What are the social, economic and legal causes that lead to recidivism in narcotics crimes?

STATUS AMONGST FAMILY

Table 9 presents the status of the recidivist amongst his family.

TABLE 9: STATUS OF RECIDIVIST AMONGST HIS FAMILY

Status	Number	Percentage
Spoiled	9	33.3
Outcast	2	7.4
Neglected	1	3.7
Others	12	48.1
Total	25	95.5 %

MARITAL CIRCUMSTANCES OF RECIDIVISTS

The marital status of recidivists is given in Table 10. Major causes for returning to narcotics crimes were marriage (22.2%) differences and others (25.9%). Other causes were insignificant.

TABLE 10: MARITAL CIRCUMSTANCES OF RECIDIVISTS

Marital circumstances	Number	Percentage
Marriage differences	8	22.2
Doubts about the wife	1	3.7
Encouragement from the wife	1	3.7
Lack of suitable atmosphere	1	3.7
Others	7	25.9
Total	16	59.2

STATUS OF RECIDIVISTS AMONGST FRIENDS

Bad company and friends rates high for causes of narcotics recidivism, as declared by 14 inmates (51.9%), as shown in Table 11.

TABLE 11: STATUS OF RECIDIVISTS AMONGST FRIENDS

Status	Number	Percentage
Bad company	14	51.9
Refusing advice from good friends	4	14.8
Revenge from friends	3	11.1
Others	3	11.1
Total	24	88.9 %

THE EFFECT OF EMPLOYMENT CIRCUMSTANCES ON RECIDIVISTS

Table 12 shows the effect of employment circumstances on recidivists to narcotics crimes; seven inmates (29.9%) stated that there exist other effects than those mentioned.

TABLE 12: EFFECT OF EMPLOYMENT CIRCUMSTANCES ON RECIDIVISTS.

Employment Circumstances	Number	Percentage
Opinion of direct boss of recidivists	2	7.4
Opinion of work colleagues to recidivists	4	14.8
Future consideration at the job	5	18.5
Other effects	7	25.9
Total	18	66.6 %

INCOME AND AVAILABILITY OF MONEY

Table 13 shows the relative income and availability of money to narcotics recidivists. 12 inmates (44.4%) were of middle income group, six only stated that they have high income and can afford drugs.

TABLE 13: LEVEL OF INCOME OF NARCOTICS RECIDIVISTS

Money Availability	Number	Percentage
Available	6	22.2
Average	12	44.4
Short	9	33.3
Total	27	100 %

EMPLOYMENT AVAILABILITY

Table 14 shows that the availability of employment in respect of drugs criminals, and the questionnaire showed that 37% of the total criminals are not employed, that means that they are unemployed, and that 55.6% of them were employed in various occupations.

TABLE 14: EMPLOYMENT OF NARCOTICS RECIDIVISTS

Employment	Number	Percentage
Employed	15	55.6
Unemployed	10	37
Total	25	92.6 %

DESIRE FOR IMMEDIATE WEALTH AND A LEADING ECONOMICAL POSITION

As shown in Table 15, 62 percent of recidivists in narcotics crimes do not have a desire for immediate wealth, whilst 25.9% do. Concerning the objective of returning back to narcotics crimes, 18 inmates stated that they do not have a desire for leading economical status amongst friends, on the other hand six inmates responded that they do.

TABLE 15: DESIRE FOR IMMEDIATE WEALTH AND OBTAINING LEADING ECONOMICAL STATUS

Cause	Yes		No		Total	
	No.	%	No.	%	No.	%
Desire for immediate wealth	7	25.9	17	62.1	24	88.9
Desire for leading economical position	6	22.2	18	66.7	24	88.9

LEGAL CAUSES

Table 16 presents some of the legal causes of committing narcotics crimes, the negative responses for the legal questions were higher than the positive ones. It is worth noting that 12 inmates (44.4%) indicated that they believe that the imprisonment period is not compatible with the charge faced. Eleven inmates (40.7%) indicated that there is weakness in the procedure of final investigation (courts).

TABLE 16: LEGAL CAUSES FOR RECIDIVISM IN NARCOTICS CRIMES

Cause	Yes		No		Total	
	No.	%	No.	%	No.	%
Gaps in the law	6	22.2	20	74.1	26	96.3
Weakness of first degree sentences	6	22.2	19	70.4	25	96.6
Weakness of appeal sentences	9	33.3	17	62.1	26	96.3
Weakness of preliminary investigation	4	14.8	20	74.1	24	88.9
Weakness of final investigation (court)	11	40.7	14	51.9	25	92.6
Unsuitability of punishment	12	44.9	13	48.1	25	52.9
Deduction of time served	6	27.2	19	70.4	25	92.6
Other Reasons	—	—	—	—	—	—

OTHER CAUSES

In the questionnaire provided for mentioning other causes, the inmates pointed out:

1. Strict control over smugglers and drug dealers.
2. Psychological therapy to the addict without punishment.
3. Lack of working opportunities for ex-convicts causes their return to narcotics crimes.
4. The presence of drugs inside Kuwait is a sign for slack inspection at the borders.
5. Differences and discrepancies between sentences in Kuwait.
6. Lack of entertainment facilities.

SUMMARY

The fourth chapter presented the actual results of the research, which included the results of the first section (demographic data), the second section (technical details), the third section (social causes), the fourth section (economical causes) and the fifth section (legal causes).

CHAPTER FIVE
SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

INTRODUCTION

This chapter contains an exclusive summary of previous chapters in addition to the conclusions of the research and recommendations, which combine both the recommendations of the research in addition to recommendations for further studies to compliment this project.

SUMMARY

This research has been designed to determine and analyze the most important social, economic and legal causes for recidivism in narcotics crimes. It is hoped that such determination and analysis shall assist decision makers to:

1. Realize the extent of the problem on the social, economical and legal frontiers.
2. Draw up planning policies and preparation of trained staff to deal with the problem.
3. Evaluate the existing programs aimed at limiting or decreasing the habitual narcotics problems.
4. To determine the requirement of security and drug combat forces.
5. To determine the social, economic and legal causes for recidivism in narcotics crimes.

In addition to that, the research sought to obtain certain personal and technical characteristics of narcotics recidivists.

A carefully prepared questionnaire has been used after intensive literature review and direct consultations with practising professionals. The questionnaire is composed of five sections: demographic data, technical details, social causes, economic causes and legal causes of recidivism.

A sample was chosen from Central Prison inmates. It was expected that fifty inmates would be subjected to the questionnaire. Only 27 of them managed to participate (54 percent), others were unavailable. The data was sorted out and analyzed manually.

The first and second part of the questionnaire asked narcotics recidivists to provide some personal and technical information, that will help to formulate a response to the following question:

What are the available personal and technical data about recidivists in narcotics crimes?

The response gave clear indications that all recidivists were males, 66.6 percent of whom were between 26-35 years of age. Fifteen of them (59.3%) were socially stable, nine (33.3%) were single, nineteen (48%) were employed by the private sector while six (22%) had private business. Five inmates (12.5%) were unemployed. Eight (29.6%) had a monthly income between KD 301-400 while half of that figure had a monthly income not exceeding KD 200.

As far as the technical details are concerned, sixteen inmates (59.2%) committed narcotics crimes more than two times. The most recurrent charges were abuse than dealing. Most of the recidivists had been sentenced between 2-10 years' imprisonment.

The third, fourth and fifth sections have been designed in order to answer the following question:

What are the social, economic and legal causes for recidivism in narcotics crimes?

From the answers furnished by the inmates, thirteen of them (48.1%) indicated that there were other reasons than the ones given by the questionnaire (spoiling, outcast, or ignored) which caused them to return to crime. Only nine (33.3%) said that they were spoiled at the house, seven (25.9%) indicated that they had marriage differences while 14 (51.9%) refered the recidivism to having bad friends. On the employment front, seven (25.9%) said that there were other reasons than the ones given in the questionnaire (opinion of the direct boss or colleagues and the future considerations of employment).

As far as the economic causes are concerned, twelve inmates (44.4%) said that they had average financial resources, nine (33.3%) had limited resources, while six only (27.2%) indicated they had an abundancy of financial resources. Fifteen of the inmates (55.6%) were employed before imprisonment, whereas ten (37%) were unemployed before being arrested. Most had negative response for considering the desire for immediate wealth and leading position between friends as a cause for recidivism.

For the legal causes, the inmates described the law as flawless, and sentences were not weak at first or appeal levels, that the investigations were fair especially the preliminary ones. There was some hesitation about the final investigation. Many indicated that the punishment is not compatible with the crime. They have discarded the reduction of time served as a cause of recidivism and provided some other consideration as detailed in chapter four.

CONCLUSIONS

Both the conclusions and recommendations of this research shall prove to be useful to decision makers and planners in combating drugs and narcotics. The knowledge of the different causes (social, economic or legal) for recidivism is an important tool for the drug combat department in order to perfect its job and find means to limit the widespread of narcotics abuse in general and recidivism in particular.

SECTION 1 - DEMOGRAPHIC DATA

1. The obtained information indicated that most of the recidivists were between 26-35 years old, mostly married and whose education level is either preliminary or intermediate.

It may be concluded that although most of the recidivists were socially stable, they had problems related to age and culture. The 25 - 35 age group is characterized with youth and incomplete experiences about

marriages and family affairs. It is a transition period between youth and maturity and behavioral fluctuation could be expected. The situation might aggravate due to a poor cultural background and sound level of education which affect the process of critical decision making. Such an individual could easily fall for professional narcotics groups. We, therefore, appeal to the agencies concerned with the well being of youth at this age group to provide suitable guidance that keep the individual apart from falling into drugs abuse. The powers and resource of the youth should find a more convenient means of production.

2. The research indicated that most narcotic recidiivists were government employees (public sector) and their monthly salaries ranged between KD 300-400.

This leads to the conclusion that such recidivists have had stable jobs. It is therefore recommended that public sector employees should be encouraged to involve themselves in higher studies rather than allowing them to be promoted on seniority basis only. A scheme that gives incentives and bonuses for hard working individual should prove quite useful in this regard. It is hardly surprising that dull continuation of the same job creates some kind of gap that could be used by the employee for unlawful behaviour.

SECTION 2 - TECHNICAL DETAILS

1. The collected information indicated that most recidivists have been arrested more than once for abuse and dealing charges, and they had been convicted and sentenced.

This leads to the conclusion that there exist motives and causes that helped them to return to narcotics crimes, including family upbringing, marriage differences, bad company, relation with superiors at work, employment condition and financial resources. It is postulated that if such causes were known, suitable solution can be found to prevent recidivists from returning to narcotics crimes. Therefore, we advise the authorities concerned with the youth to indentify their needs and study their social and economic conditions.

SECTIONS 3, 4 AND 5 — SOCIAL, ECONOMIC AND LEGAL CAUSES

1. The social causes for recidivists focused on the relation of the perpetrator with his family (such as spoiling or else ..), marriage differences or others, bad company, doubts about the future and other effects.

It is concluded that although most of the recidivists in narcotics crimes were socially stable, there were some disturbances that generated a space for meeting bad company. We therefore recommend that special agencies be set-up to provide social services during such condition in order to help the individual and safeguard against nap hazardous decisions. Such an agency could be a separate department under the Ministry of Labour and Social Affairs, or any other government office.

2. The economic causes indicated clearly that narcotics recidivists were employed by the public sector and their financial status is average and they had no desire to make immediate wealths.

It could be infered that most recidivists had stable jobs. This stability was accompanied with incentives to prove oneself. We suggest that employers and agencies concerned with employment should be encouraged to act fairly so as not to push the employee to search for other means to reach his career wishes and requests through exploiting his position. As far as the unemployed are concerned, we suggest that responsible authorities help them to find suitable employment in order to avoid the creation of negative attitudes in the society that cause further offences.

3. Concerning the obtained results of legal causes, they showed that recidivists had slight observations and discomfort regarding the weakness of final investigations (courts) and unconformity between charge and punishment. Other causes such as gaps in the law, weak sentences of the first degree or appeal, weak initial investigation and reduction of time served, were just individual cases.

It is concluded that most inmate expressed satisfaction about legal matters except the imprisonment period and weak final investigation. These remarks should be observed for improvement.

RECOMMENDATIONS

After careful review of the results of the study, we present the following recommendations which could be useful for recidivists, decision makers and the Kuwaiti society in general.

1. Giving consideration to the age groups in the productive age through diverting their resources and capabilities to more socially fruitful works.
2. Identifying the requirement of the youth for passing leisure time and entertainment requirements.
3. Promotion of cultural and religious awareness amongst this group to save them from responding easily to the incitement of drugs.
4. Creation of an atmosphere of understanding for the harm and consequences of drug abuse.
5. Consideration for public employees and creation of incentives (moral, material) and encouraging higher educational standards.
6. Develop the relationship of the employee with his job and colleagues in respect of production and hardwork not in respect of leisure time.
7. Review the conditions of recidivists during detention and taking these conditions into account during trial.
8. Determination of the social causes of recidivism, so that concerned agencies could act to protect the youth from aberration.
9. The employee should be given his professional rights so as not to revert to unlawful means to reach his desires.
10. Improvement of criminal law regarding conformity of crime and punishment.
11. Finding means to treat the recidivists in narcotics crimes.
12. Increasing trained and qualified staff at the drugs combat department.
13. Giving consideration for the economic conditions of persons apprehended for narcotics charges and assisting them to find a source of income to support their families and return to the natural life.
14. Paying attention to the legal aspects of the drug problem and creating qualified personnel at the attorney and judicial levels.
15. The creation of a separate attorney and jurisdiction for drugs cases, similar to juveniles.

RECOMMENDATIONS FOR FURTHER STUDIES

This study was a first step towards understanding the problem of recidivism in narcotics crimes. We would like to take this opportunity to table some of the problems and subjects that are related or complementary to this study.

1. Survey the problems facing the recidivist.
2. Study the factors and conditions other than social, economic and legal.
3. Evaluate the criminal law and its suitability to the conditions and factors surrounding recidivism.

4. Study the capabilities and efficiency of security forces in prohibiting drug dealing and pushing.
5. Study the potentials for a strategic co-operation between Gulf Council States to limit the drugs phenomenon in the region.
6. Study the methodology employed in arresting drug perpetrators for improvement and development.
7. Study the effect of education and upbringing on recidivism in narcotics crimes.
8. Study the effects of the family on recidivism.
9. Study the effects of training and rehabilitation on reducing recidivism in narcotics crimes.
10. Study the economical effects for recidivism in narcotics crimes.
11. Study the role of rehabilitation establishment in reducing recidivism.
12. Study the comparison between attitudes of recidivists and attitudes of detainees in narcotics crimes.
13. Study the relationship between leisure time and the vulnerability of taking drugs.

DEDICATION

The Research team has the pleasure to dedicate this humble work to H.E. Minister of Interior.

ACKNOWLEDGEMENT

At the request of the Director General of the General Department of Criminal Investigation, the Research and Studies Department shouldered the responsibility of undertaking this research project,, entitled "Reasons of Recidivism in Narcotics Abuse Crimes". The methodology of the research and writing of the final report here was supervised by Dr. Ismael Nassrallah. Captain Hamad Al Serrayyeh of the Narcotics Department at the General Department of Criminal Investigations, participated in development of the project idea and preparation of the questionnaire form and its application. Researcher Najat Mohamed Hassan Al Salem of the Research and Studies Department, applied the questionnaire and performed the statistical operation required for the project.

At the conclusion of this assignment we praise God for his guidance in finishing this work. We also would like to express our gratitude for the good efforts exerted by officials at the Central Prison Department, notably: Lieutenant Colonel Badr Ali Hassan, and Major Saad Abdullah Al Saeed, and the other officers and assistant officers and personnel at the Central Prison. We would like also to extend our thanks for the officers who helped to apply the questionnaire, most notably: First Lieutenant Saleh Fakhri Al Rashidi, First Lieutenant Abdullah Ibrahim, and First Lieutenant Fawzi Al Shayeh, and to the social workers: Mohamed Al Thafiri, Farhan Al Anzi, and Faleh Al Adwani, and to all the inmates who co-operated in the application of the questionnaire.

We hope that this research shall prove fruitful and shall be a good start for similar research projects in the future.

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APPENDICES

See the Arabic Text of this paper.

CHAPTER III
PLENARY LECTURE

1. CRIME: PREVENTION AND TREATMENT
   Prof. Dr. Ahmed Khaleefa
2. DISCUSSIONS *(Not available in English).*

Bulletin of Islamic Medicine, 5: (90-96), 1988.

CRIME: PREVENTION AND TREATMENT

Professor Dr. Ahmed Khaleefa
EGYPT

There has always been a tendency to strike a link between the concept of crime and the concept of sickness on the ground that the criminal's behavior is a sick behavior and not a healthy or sound behavior. No doubt this link leads to inaccurate results in interpreting crime and in drawing up preventive and punishment policy. It also affects the theory of responsibility. Moreover, this may encourage a wrong trend namely to search for the virus of crime in society similar to the search for the virus causing disease which is very far from the reality of crime and the criminal, the criminal being ultimately the making of the society where he lives.

Consequently, there exists no specific vaccine to prevent crime. It is not a virus nor any other one reason which causes crime. All views which attempted to attribute crime to one factor namely: ignorance, poverty, organic or psychological disturbances, broken family or bad example or bad mass-media or any other one reason, all these attempts failed and the general conviction among researchers now is that the crime phenomena are related to various roots which interact in a certain environment and certain circumstances which cannot be restrained and which finally generate the criminal behavior.

On the other hand, the spread of crime can be described as epidemic. In fact, the crime epidemic has spread widely and largely in modern times and its characteristics have changed more than in any other time in the past. The number of victims has also multiplied, reaching many folds more than the victims of any epidemic. It jeopardizes the whole society and exposes its interests, welfare and destiny to danger and deterioration. We affirm this even without coming close to the drug problem which has plagued humanity. The crime is sweeping all modern societies and is affecting them so seriously and deeply that sometimes the integrity of the democratic basis and human rights are jeopardized and the quality of life is threatened.

Criminal behavior, however, is woven in the fabric of the society. Since the economic and social systems and situations are ever-changing, this anti-social behavior is likewise changing. There is a continuous interaction among the elements and the economic and social relations which lead to the disappearance of forms of criminality or their variation or the appearance of forms of criminality or their variation or the appearance of new patterns of deviation.

This disproves the old traditional view of the criminal as a special type of mankind which gave the crime a strong mark of mysticism. This view is no more valid in the light of the new concept which regards the criminal behaviour as alluvion, a result of struggling waves and currents. Hence we no more regard the criminal as a unique creature who is different from other citizens because criminal factors are basically inherent in the community and they have moved away from the individual level to the social and economic level and were capable of entrapping a larger number of victims.

We have already left behind the Lombrosian logic which identifies the criminal with his nature, and we began to realize that each person is liable to turn into a criminal, because deviation and crime are a dynamic and varying aspect of the course of life; human being traits may themselves socially elevate him or may qualify him to commit a crime. The study of crime then, is the study of the individual in a dynamic changeable society. Consequently, all our concern for combatting crime and studying it should be geared to the study of patterns of the changeable behaviour and their relation to the social conditions and social functions as each socio-economic change may bring about new patterns and forms of deviated behavior related to new elements which move to the image or new interaction with these elements. In one word, we have to minimize our view of the crime as a mystique and regard it rather as a critique of society. This will lead us to turn our attention to the community itself in order to discipline it as much as possible so that no more deviation or mal-adjustment may develop as a result of its change and development.

To sum up, the old concept of crime states that criminals are a special isolated group whom we should contain and try to get rid of, while the new or modern concept states that crime is the destiny of mankind just as drinking and eating, and it changes continually on new innumerable horizons which cannot be avoided. It is the duty of the community to exert every effort possible to alleviate the burden of crime from the society in order to achieve a better quality of life.

The concept of crime is very wide and varied, although the traditional trend is to think of the traditional crimes whenever the word crime is mentioned. We immediately think of murder, rape and other similar offenses which some criminologists call natural crimes, that is, the crimes that exist in every community and at all times and places. Yet, the scope of crime has much widened due to the continuing complexity of human society, the idea of criminalization rooted in religious and moral teachings has diversified so sharply that it has come to include many deeds for which we can find no religious or moral roots. Laws are enacted on the bases of balanced interests in a particular community at a particular period. Some deeds may even be excluded from criminalization even if they go against morals and conscience, such as confining the scope of crime concerning sexual acts in many legislations to rape and forced sexual relations only.

At any rate, what makes a certain act a crime is eventually the will of the legislator who represents his community in the sense that the crime is the creation of the penal law, i.e. it is a legal reality. This does not deny the fact that the will of the legislator expresses the will of the community as it is not separated from the community beliefs and feelings. Consequently, the crime is a social reality, too, which is set up by the legislator who is not working in a vacuum, but moves under the pressure of social and economic philosophies, ideologies and fctors. However, we should admit that the law sometimes lags behind the social reality or vice versa.

Undoubtedly, the modern forms of crime have become more complicated and more pervasive as well as more rational i.e. more calculated, purposeful, rather than a slip to crime. In addition, crime has taken organized forms with strong international and influential gangs. The crime, in its present form, is no more only associated with the poor and the suffering people as it used to be when the penal law was once called the Law of the masses. Criminal acts are now, as well, the acts of the élite, the wealthy and influential people.

Crime, then is no longer the traditional form which people have known and have associated with backwardness. In fact, crime is not connected with underdevelopment nor development or high standard of living or education standard. Ironically, crime may occur less in very backward societies or in stagnant ones where no elements of development, promotion or social change take place. Once this occurs, the result will be the imbalance of relations, the emergence of deviated behavior which may then be attributed to disintegration of values, a matter which is not so evil as it might be sometimes an introduction to social and economic development.

We come to realize now that the crime is not the by-product of wants and needs in all cases as there is the

criminality of welfare and excessive wealth which tempt people to act with irresponsibility and create feelings of greed and indifference.

We repeat then that criminals are not a unique set-up or special category but they are those persons where factors, circumstances and chances gather and interact to drive them to deviation.

We wish to affirm in this connection that there is a certain parodox: the development of society and growth of economy bear within their folds the seeds of inadaptability and deviated behavior, because it is only the state of stagnation that ensures that crime remain unchangeable in quantity and type. Consequently, economic and social development is accompanied to a great extent with crime and deviation which influence the quality of life, just as industrial production results in harmful wastes which lead to pollution of the environment. This means that the best way for general prevention against crime, the criteria judging the success of the policy, is to have a social defensive policy that goes hand in hand with development policies in an attempt to minimize all forms of social waste.

This does not mean, however, that we blame the process of national development and hold it responsible for crime. The socio-economic development, as the spread of education and industrialization, reflect a natural development, but there are economic and social earthquakes which disturb the necessary balance between social and economic development. This, we witnessed clearly in the flow of oil wealth which caused a socio-economic revolution in the Arab region, the results of which are not all welcome. This enormous wealth has not led to the improvement of the quality of life in the Arab region inspite of the astonishing rise in income and the higher standard of living.

The social change which our modern era witnesses and its quick tempo is beyond questioning. The scientific discoveries, technological achievements and development of means of communication have affected human thought, the productive and economic capacity and behaviour in general. This has left apparent prints on human thinking and shaken old interests, encouraged man to break away from all the clinches and dogmas that had dominated his thoughts for long periods and influenced deep-rooted beliefs including his opinion on woman, sex and race. This great path which humanity went through in the last two centuries has, no doubt, a great effect on human behaviour and the meaning of deviation, crime and sin.

To begin with we say that the West had known freedom of thought as a result of waving the domination of the church and the engagement in the fields of science, and philosophy. Thus, the 19th and the 20th centuries have witnessed more freedom and more concern for the individual rights vis-avis authority and society. This atmosphere of freedom has led to the liberation of nations from slavery, oppression and colonialism in the light of the right of self-determination and principles of equality. From the economic point of view, the aura of free economy brought about the middle class and capital, while playing down the influence of feudalism. The emergence of the free economy and the dwindling of feudalist tradition have inevitably affected values and behaviour and led to the emergence of new values. We can also say that it was the beginning of the liberation of youth from the domination of elders as well as a signal for the liberation of woman and her setting free from tradition and beliefs which previously put her in an inferior status to man.

In addition to that, we have all that the 20th century - in particular the second half of it - had brought about: the astounding successive scientific discoveries, the communication and transport revolution, the extinction of the remaining thoughts based on dogmas and fixed ideas and the surge of utilitarianism, pragmatism and materialism, overshadowing any moral considerations. Views and concepts are in conflict and struggle around the remaining belief in the existence of sacred and eternal principles and values which should not be infringed or touched upon. This modern ideological atmosphere in which most of the world mostly lived during the past half century, has deeply affected behavior. It might be that the excessive abandon and destruction of the

prevalent morality has been responsible for the emergence of counter-movements which call for the rejection of the present, denouncing it comprehensively and calling for the return to the past and glorifying it.

At this stage, economic crimes have emerged. We do not mean here by economic crimes, the usual crimes against property such as theft, fraud and embezzelement. We mean the serious crimes which have an effect on the economic system and which led to the involvement of people of status, not the commoners, in the field of crime. Today, the crimes of the weak are less important compared to the crimes of the more capable, influential and money holders and that is due to the complexity of economic life, the large loots and the ability to escape and evade any punishment, as well as the high social qualities enjoyed by the new offender.

The economic crime includes offenses committed in the course of the so-called open-door policy which lacks organizing and sufficient legal regulations and also crimes of black or invisible economy. They are deeds of long-term effect which shake the basis of economic life and revolve around the loopholes, make use of contradictions and strive to buy people's conscience. They grow even more serious where there are no strict systems and clear firm laws to regulate the economic activities of individuals and organizations.

It is well known that the economy moves between two pivots or axis, one is absolute freedom and the other is state controlled economy. There are many models which lie between these two pivots. Not all those models could be suitable for every community, and each community has to select that which is most convenient or else the door will be wide open to fraud and criminality.

We cannot disregard in this connection the crimes of companies and economic institutions as they are undoubtedly, more dangerous and more far reaching than all individual crimes combined, leading to multiple losses of public and private property. There is no limit to schemes and manipulations which some organizations resort to plunder the state money and people's savings. These crimes generally fall within the scope of the so called white-collar crimes, which are usually known to be crimes committed by bureaucrats, professionals and by people of higher positions, the difference is that these crimes are committed by institutions and not by white collar individuals such as embezzlement and use of computers to commit crimes.

In this scope fall the crooked business which deceive investors and share-holders, launch deceptive advertizing, cheat consumers, tax evasion and close deals deceitfully and illegally.

Economic crimes, however, have reached such huge proportions that calls for a special code of law for economic crimes. Also there should be measures and special courts to deal with the most serious of these crimes to put an end to economic sabotage and destruction.

As to the so-called businessmen or Hommes d'Afaires crimes, they are interrelated to a large extent with the scope of economic crimes. The reference to the white collar crimes was a reaction to the old view which associated crimes with lower classes and common people of blue collars and manual workers. But at present the word white collar is not enough to define the extent to which the situation has developed, as the gravest of crimes are committed at the highest levels. Today, the talk is about crimes of businessmen and abuse of influence.

One specific form of business crimes which is widespread at the present time is the use of bribery in all its shades to obtain concessions and contracts with governments or organizations. Rarely do big business or the conclusion of contracts get through without resorting to one or another kind of bribery; some businessmen go to the extent of saying that if they do not resort to these means, they will never be competitive.

It is obvious that business crimes are the kind of crime for which we look less for factors in the criminal's character or education, upbringing, environment; it is the individual own choice and will. In fact, corruption exists when there is free competitive economy. It is also present in the centrally controlled economy. Penal

laws in the Eastern countries stipulate the strictest penalties for economic crimes such as smuggling, speculation on prices of essential goods and serious negligence in business management. These penalties can be more severe than with crimes like murder, theft, and sexual crimes.

Business crimes include higher social categories such as the heads of departments, companies, lawyers, politicians, physicians, engineers and directors. All these are involved in white collar or abuse of authority crimes. This is the reason why we see the prisons housing types of people other than those it used to receive.

Yet there is a specific level of bribery in particular in poor countries as India and some Middle East countries as Egypt and in South America. This is the bribery or "bonus" which has to be or else no business could be accomplished paid to the responsible official or worker. The work sought to be accomplished is legal all right, but it cannot get started before paying this bribery. This prevails in the governmental and non-governmental circles. Some see that this small "bonus" is normally a raise which the official or worker gets to improve his income to enjoy a reasonable standard of living.

Besides businessmen's crimes, it is necessary to point out abuse of authority crimes in particular. These happen under all systems but they aggravate if legal and political situations allow protection or immunity to influential officials, thus, encouraging further crimes.

It is not to be understood that the crime is connected to a specific economic system as it is not an attribute of capitalism nor planned socialist economy. Under both systems crime exists even if its features differ. Nevertheless, we can say that counterfeit capitalism or socialism can account for it because in the name of capitalism or free economy a kind of wild economy i.e. brute unorganized capitalism, could prevail abolishing equal opportunities. Socialism could be a name concealing state capitalism where all offences and all kinds of exploitations are committed in the name of social justice. Undoubtfully, this forgery accompanied with all disequilibrium in the balances of social justice, equal opportunities, and human rights are fertile land for the existence of all kinds of deviation, corruption and rebellion.

One more word remains to be said about terrorism. It is one of the epidemics of modern society. It grows stronger and spreads further, gaining every day new ground and violating new border. Bombs are hurled, buildings, houses and transport means are blasted, districts are blown up, hostages are seized and villages with their children, women and old people are slaughtered. This is a special form of violence, a vicious child of an astray parent and a sign of deterioration in human feelings, justice and respect of law.

As for violence, it is a wide-range expression and it means using force and ruthless means. Although not all violence is terrorism we can regard all that is terror as violence. There is no terrorism unassociated with violence. Moreover, those who commit terroristic acts do not care who gets harmed innocent or no innocent.

Terrorism cannot be justified as we sometimes do as regards violence. Violence could be legitimate in case of self defence, counterattack or liberation of land and country but terrorism cannot be justified even if it claims that it has a cause and that the end justifies the means. All this does not conceal the fact that terrorism sacrifices innocents and even if it starts with a noble target it quickly ends in cowardliness, baselessness and defiance of all what the community, law, mercy and human rights represent.

Even when wars break out between states the citizens and innocents are protected by rules of the international law and treaties are concluded to this effect to protect captives of war, sick and aged people even if they were foes. But even this civilized attitude during war is not observed or respected by terrorism during peace.

Terrorism usually indicates a political context but there is terrorism free of political tint, i.e. pure criminal attitude for the sake of material gain such as the attempt of a criminal gang or group to terrify people by acts of

killing and brutality without discrimination in order to realize material gains while not working under any slogan or for any certain cause. A similar thing takes place on the international arena at the hands of international gangs which carry out terroristic acts such as the Mafia gangs, the drug gangs and slave trade gangs. In this case violence is usually directed towards certain people and money in deterrence and rervenge.

At the political level, when terrorism occurs and becomes the language spoken by some, then the thing that is most cherished by a people namely its democratic rule and sovereignty of law are at stake at the point of the gun, triggering out the worst in the human instinct.

Some may claim that individual and organization's terrorism is the result of terrorism of the state and its system which strive on despotism. This may be true to some extent but the dimension of terrorism at present indicates that it has become a common denominator in democratic and non-democratic societies as well.

We should, however, emphasize the difference between violence and terrorism on the one hand and the people's legitimate fight for liberation and self-determination on the other hand. The opportunist forces in the world aim at farnishing the people's national struggle which is the people's right and duty by calling national resistance terrorism as if these subdued people should submit to slavery, oppression and subjugation. This is a flagrant example of political hypocrisy in search for interests and resorting to the use of double standards in similar situations.

On the other hand, we have to differentiate between terrorism and organized crime. The organized crime has no cause and is perpetrated by those who have chosen crime as their profession or economic activity, they do not claim heroism and they are usually not suffering from any psychological illness. They are characterized by a high mental and organizational capability and are directed by a businessman mentality simply seeking power and wealth.

The modern society now knows the phenomena of organized crime, that is crime as a job business which yields great profits. The criminal is no more the victim of circumstances or family disentegration or bad bringing up but the criminal chooses with full awareness the criminal activity as a profession and work. Strong powerful and overseas gangs are formed to trade in anything ranging from smuggling goods to slave trade, to arms and drug trafficking.

Terrorism remains an international modern epidemic. This international character should urge the international society to unite to combat this epidemic and to conclude an international agreement which considers terrorism in itself an international crime such as genocide, apartheid. Cooperation among states should be established in the best form to implement human moral commitment to pursue terrorism and terrorists at the world level.

We have to think what the crime would be like in the 21st century. Certainly, the forms and volume of the crime will change in the light of the socio-economic changes. The age of the criminal may drop and women activity in the crime field might increase due to the women's progressive involvement in public life and economic activities.

It is expected that the trend toward crime as an institutional activity would be deepened and offenses committed by organized groups whether criminal groups, public organizations, official or private organizations exercising illegitimate activity in affirmation of what we note today of corruption of public organizations, companies and private business.

In brief, it seems that a profound change should take place in (crime producers). We shall not be surprised to find that bodies combatting crimes and agents producing crimes will be mixed together; that is the involvement of law-enforcement authorities in committing criminal activities.

It is impossible to imagine that the world would rid itself in the up-coming century from crime, such a thinking is naive and can convince no one. In fact the opposite may be true. It suffices to imagine the strength and power of capital in dirty hands, concentrating at home and abroad and beyond borders, corrupting the influential people, hitting the economy or causing it to deteriorate thus leading to further concentration of power and wealth used as leverage for monopolization, fraud and illusionary projects as well as speculation and shaking the financial confidence resulting in poverty, inflation, unemployment and corruption.

In conclusion, we have presented general views on crime - its prevention and treatment. The special nature of the society is shown through the study of the criminalization and punishment policy in any society. The penal law sometimes wears the gloves of a surgeon who seeks to cure and treat or wears iron gloves which means organized revenge and brutality in the name of the law. The whole matter depends on the general policy of each particular society. In fact the criminal or penal system is but a social system reflecting the advantages and disadvantages of the macro-social system. Anyone who has to study crime and punishment should focus on the model of society case by case.

CHAPTER IV
PAPERS PRESENTED

1. CURRENT ALCOHOL RELATED PROBLEMS
   Dr. Nabeel S. Al-Taweel
2. IMPACT OF MORAL LICENCE ON PUBLIC HEALTH
   Dr. Maher M. Hathout
3. AIDS: THE PROBLEM OF CONTEMPORARY WORLD AND A FUTURE ISLAMIC VIEW.
   Dr. M.H. Wahdan
4. THE RESPONSIBILITY OF ART *(Not available in English)*
   Hassan Yousuf
5. DISCUSSIONS *(Not available in English)*

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CURRENT ALCOHOL RELATED PROBLEMS

Dr. Nabil S. Al-Tawil

PAKISTAN

INTRODUCTION

Alcohol is the oldest and most widely diffused intoxicating substance known to man[1].

Reports from a wide variety of countries indicate that health damage and social disruption due to drinking are greatly on the increase[2], especially in developing countries where alcohol has had a particularly devastating impact in recent decades as a result of a considerable increase in consumption. The most important lessons emerging from accumulated research is the positive association between trends in consumption and trends in alcohol related problems: physical, moral and economic; similarily, trends in production and trends in consumption are obviously linked[3].

The commercial production of alcohol occurs mainly in the industrial countries. Following the stabilization of the market at a certain level in developed countries, much of the output in alcohol is now being exported to the Third World. The most important agents marketing alcohol in the poor states of the Third World are the multinational companies. Such companies even contribute to the financing of local industries engaged in the production of alcoholic beverages in Muslim countries as well as others. The following gives us some information on the tragic situation now existing in Muslim societies:

1. The consumption of beer in Nigeria — both imported and locally produced — reached 160 million litres in 1970 and rose to 448 million litres in 1976[4].
2. In the Cameroon the per/capita consumption of beer rose from five litres in 1960 to 33.1 litres in 1981[5].
3. While nearly 8.6 million litres were produced in 1973, 17 million litres of beer were produced in Sudan during 1975-1976. The latter figure represents much less than was consumed in that period[6].
4. The total production of wine officially recorded for 1980 in Morocco, Algeria, Tunisia and Turkey was of five million hectolitres[1].
5. In addition to the importation of alcoholic beverages to Indonesia and Malaysia, subsidiaries of multinational companies produce such beverages locally.
6. A number of Arab states in the Eastern Mediterranean region produce alcoholic beverages in nationalized industries and consequently have economic interest in promoting the marketing and consumption of such drinks.

The state of affairs now prevailing in the poor "South" — where the majority of the population of Afro-Asia is Muslim — has led research workers to predict catastrophic effects of a greater magnitude than those

currently prevailing in the West. Western experts themselves express the opinion that the most important consequence of the universal spread of Western culture has been the adoption of the drinking habits of the West. Having had no experience with alcohol, the process of acculturation completely destroyed the traditions and values of these indigenous populations[7].

Dr. Kendell, the Psychiatry Professor of Edinburgh University, wonders why the Western countries prevent the trading with opiates, cannabis and other intoxicants while they promote the trade of alcohol; even though the latter is also an intoxicant, a carcinogen and toxic to nearly all tissues of the human body. He explains this curious and contradictory attitude by the fact that alcohol happens to be the preferred intoxicants of Europeans and Americans of European descent as it is a prerequisite for Judeo-Christian festivities. To this effect, Walsh and Grant[1] state:

> The concept of intoxication plays an important part in religious thinking in many different cultures, and it is common for particular religions to accord it special significance; the frequent mention of wine in the Bible and its central place in subsequent Christian practices contrasts with the asceticism and the warning against its use in the "Koran".

The Ill Effects of Alcohol Intake

Dr. Samuel Hynd says: alcohol is destroying millions more than the famine in the African "Sahel"[8]. While in some European countries one out of every three beds in general hospitals is occupied by a case of alcohol related problem[9], it is confirmed now that regular drinking, even in moderate quantities, damages almost all tissues and organs of the body: brain, nerves, liver, muscles, pancreas, kidneys, heart, stomach, intestines, sexual organs and their function. Alcoholic liver disease (cirrhosis) is now the chief cause of death among middle-aged men in many developed countries. One reason why heavy drinkers die earlier than other people is high blood pressure caused by the effects of alcohol. There is also evidence that even moderate amounts of alcohol, if taken regularly, considerably increase the risk of cancer of the mouth, esophagus, pharynx and larynx as well as liver cirrhossis.

In addition, there are many emotional, psychological and mental diseases caused by alcoholism. The number of alcoholics in the USA went over the mark of ten million since 1967; with their family members, the number rises to 28 million[10]. Recent statistical data from the USSR indicates that the number of officially registered alcoholics is 4.5 million; the latter figure excludes millions of unregistered alcoholics[11]. In 1987, 8500 persons including 500 children died in the USSR as a result of fires caused by drunken individuals[12]. In the face of such a situation, Mr. Gorbaschev chose to intervene personally in a campaign against alcohol and alcoholism since 1985, without any impressive results so far.

Half of the beds of mental hospitals in the West are occupied by people suffering from alcoholic psychoses. The individual alcoholic runs a great risk, for himself as well as for his family, in developing psychological and neurological disturbances causing pain, suffering, disintegration and deprivation. On the societal level, traffic and industrial accidents and the consequent disabilities take a major toll. It is estimated that in developed countries fifty percent of the fatal accidents involve drivers who either have been drinking alcohol or taking drugs[13]. Current indications are that the rates are as high or higher in many developing countries. As for crime, surveys indicate that nearly fifty percent of cases of violence such as rape, murder and assault involve people who have been drinking shortly beforehand.

On another level, the financial loss due to alcohol intake is colossal. Suffice it to mention here that in 1979 the United States of America lost 113,368 million dollars on alcohol related problems.

It is sad to state that the Muslim community has not been spared the damages mentioned above; they are in the midst of dancing to the Western tunes. A credible Muslim researcher who undertook to study the rate of alcohol intake in the capital of his Muslim country, found that fifty percent of the youth take alcoholic beverages[14].

What is the Solution to these Problems?

Islam is simply the only refuge available to radically do away with this epidemic disease. Its ideology prohibits the use of alcohol. The Holy Koran states:

YE WHO BELIEVE
INTOXICANTS AND GAMBLING
DEDICATION OF STONES
AND DIVINATION BY ARROWS
ARE AN ABOMINATION
OF SATAN HANDIWORK
ESCHEW SUCH ABOMINATION
THAT YE MAY PROSPER

(S.V:V.90)

The Prophet Mohammad (ﷺ) said

"any alcoholic beverage is an intoxicant and all intoxicants are Islamically prohibited".

The Western experts are also aware of this fact; they call for the prevention and control of the scrouge of alcohol by total abstinence, which, they say, is the surest way to combat and treat alcoholism. In a leading article of the British Medical Journal, the British expert, Griffith Edwards, says that Western scientists insist on total abstinence as the therapeutic goal for alcoholics[15].

Among Western thinkers and intellectuals of this century, Arnold Toynbee[16] was surely one of the most perceptive in predicting the ravages inflicted on the Third World by alcohol introduced by the West. More than 40 years ago, Toynbee called upon Islam to lead the world in combating alcoholism and alcohol related problems as well as racial discrimination. He said:

> We can, however, discern certain principle of Islam, which, if brought to bear on the social life of the new cosmopolitan proletariat, might have important salutary effects on the "great society" in a nearer future. Two conspicuous sources of danger in the present relations of this cosmopolitan proletariat with the dominant element in our modern Western society are race consciousness and alcohol; and in the struggle with each of these evils the Islamic spirit has a service to render which might prove, if it were accepted, to be of high moral and social value. The absence of racial discrimination in Muslim societies is one of the most prominent performances of Islam.

As for the evil of alcohol, Toynbee adds, it is at its worst among primitive populations which have been "opened up" by Western enterprise:

> The conversion of the native's soul is a task to which competence of Western administration can hardly be expected to extend; and it is at this point that Islam may have a part to play..., In two of these tropical regions, Central Africa and Indonesia, Islam is the spiritual force... and this spirit may be expected to manifest itself in many practical ways. One of these manifestations may be a liberation from alcohol, which was inspired by religious conviction and which

was, therefore, able to accomplish what could never be enforced by the external sanction of an alien law"

James Baldwin[17] expressed his admiration for the Islamic way of dealing with alcohol and alcoholism in the following manner:

> ... But the miracle happens; the alcoholics change instantaneously when they convert to Islam. Islam was able to accomplish what generations of social scientists, committees, resolutions, welfare and entertainment centers failed to achieve... It is complete and total cure. Islam gained to its fold the ex-convicts who left prisons and was able to keep them away from prisons, Islam made men pure and women decent and gave them both the dignity and serenity which encircle them like a continuous light.

Islam, then, is the only inpenetrable defense against alcohol and its damage. Islam saves people from suffering in this life and the hereafter. On this basis anyone who resists Islamization of the society and state is not only ignorant but naive; and he therefore contributes to the confirmation of miseries and their intensification in himself, his country-men and his society.

A number of other practical measures necessary to add to the immunization of the believer and the *"Ummah"* should be:

1. To stop local production of alcoholic beverages in all the Muslim World and completely end their importation. It is proposed to shift from the production of alcoholic to non-alcoholic beverages thus ensuring that investors maintain their prosperous production. This solution has been suggested by all knowledgeable and concerned figures. "Grape juice ...instead of wine", is the slogan propogated by the leader of the most important Communist party in the world, Mr. Gorbaschev[18].

   This is the example we offer to those who manufacture alcoholic drinks in the Muslim World -- public and private sectors alike -- to show that there is no contradiction between the moral and health requisites, on the one hand, and the needs of the economy, on the other. Let them be assured that the implementation of Islamic *Sharia* will not result in the loss of economic profit, but will contribute to decreasing their sins while transforming their means of livelihood and prosperity from *"Haram"* to *"Halal";* and by the good grace of God they may be forgiven their past sins.

2. To reduce, or better yet to completely stop, the individual demand for the consumption of alcohol, the following measures should be adopted:

   a) The right Islamic education at home and in all educational institutions.
   b) Arrange recreational exercise for youth in cultural, sport and marshal arts activities.
   c) Provide social justice and employment opportunities for everyone.
   d) Ensure, people in general and youth in particular, to enjoy emotional, moral and physical security.
   e) Ban on any advertisement tempting directly or indirectly to use intoxicants of any sort. It is known that the mass media in the Third World is subservient -- willingly or otherwise -- to the Western media. The latter in turn is largely dominated by the Jews.
   f) Stop forthwith all Westernization processes by the rightful guidance and the revision of all programmes and curricula. Education should only be inspired from our own cultural heritage and Islamic teachings. Health education should be instituted to change lifestyles thus ensuring that children grow healthy in body and mind.

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IMPACT OF MORAL LICENCE ON PUBLIC HEALTH

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U.S.A.

Disease -- its processes and causes -- is as old as life itself. Its causes, now as at the dawn of humanity, are myriad, ranging from viruses or bacterial microbes, to larger organisms, such as parasites, to non-biological factors such as toxic substances or extremes in heat, cold, or radiation exposure. Another main subdivision of causes are the genetic diseases, varying in their mode of inheritance and penetrance, and leaving their mark not only on the patient, but on his progeny as well.

We are daily making what we consider as new discoveries in the study of disease processes and causes. However, what we are discovering is in fact age-old, and is revealed to us when and how God wills.

One important, perhaps most important, factor in determining each person's susceptibility to the various diseases centers around that person's behaviour in and of itself. Simplistically, whoever exposes himself to cold without adequate shelter, or to heat without adequate protection, or to radiation without adequate shielding, or to microbes without adequate prophylaxis, will inevitably succumb to the disease process which he has brought upon himself.

Within these vast and complicated networks of cause and effect, man toils to find ways to insure his health and protect from disease. Hence the development of the sciences of medicine and pharmacology and the practices of treatment and prophylaxis. Yet, our modern medicine, in the midst of its heroic struggle against the various parts of disease control, may have missed the whole for the parts. The "whole" here refers to the scheme of life in general, and more specifically, to the impact of one's moral system and its resultant behavior patterns on one's health. In its efforts, modern medicine has perfected laboratory tests, diagnostics, and surgical procedures which only a decade ago were unanticipated; however, one must wonder whether this technical advancement has not been at the expense of a breadth of vision which incorporates the real, and often non-technical aspects of disease production and control.

It is this current situation which gives rise to the paradoxical circumstances that as medicine is advancing, so likewise is disease spreading among our populations. In this light, we see that the role of the Muslim physician is one of dynamism and vitality, for not only is he a scientist, but he is also a humanist who empathizes with the suffering of his patients and who views himself as one of the aspects of Divine mercy extended to all humans, the moral and the immoral, the believers and the unbelievers. Such a Muslim physician, while being "state of the art", would have the breadth of vision to diagnose all the causes of a disease process, and deal with them in an effective manner rather than in merely a preaching or rhetorical style. In the west, by contrast, the role of the physician is becoming more established as a purely technical role, devoid of ethical advice or moral guidance; the role of the physician becomes merely to heal, not to teach, judge or advise.

The Muslim physician, on the other hand, sees, or should see, preventable teaching as the first line of defense in medicine. The Holy Quran teaches us this attitude of avoiding ills so that they do not befall us:

> *"PROTECT YOURSELVES AND YOUR FAMILIES FROM A FIRE WHOSE FUEL ARE MEN AND STONES"*
>
> *(S.66:V.6)*
>
> *"HEED (BE CAREFUL OF) A TEST WHICH STRIKES DOWN NOT ONLY THE TRANSGRESSORS AMONGST YOU".*
>
> *(S.8:V.25)*

The Quran, and the traditions of the Prophet (ﷺ) contain many other verses and wisdoms of the same meaning.

The Muslim physician must also realize that preventative medicine does not refer only to a narrow sector of biochemical prophylaxis, but rather encompasses the entire spectrum of human behavior, reflecting the myriad and interrelated causes of disease. To ignore the role of morality and behavior is akin to treating malaria while ignoring diphtheria, or concentrating on antibiotics while ignoring cancer.

The Muslim physician, because of his Islamic sense, indeed views disease prevention as an all-encompassing phenomenon, which can best be summarized and achieved by man's submission to God. In this way man takes the straight path. The Muslim physician sees his responsibility as helping guide to this path, not in a preaching rhetorical manner, but in a medical manner, where he honestly dissects ills to their root causes, and then reflects the parts back to the whole -- that prevention has in man's viewing himself as a responsible being, and as part of God's creation.

In this light, it is clear that the slogans of liberalism and licence do not reflect true freedom, but are only apparitions and illusions of it, leading often to ills of the body, soul and mind, which tragically "do not strike the transgressors among you especially."

However, the absence of this broad view of medicine in the west has led to two important results:

1. The isolation of the physician away from the human aspect of his patients, and his taking refuge instead in mechanical devices, equipments, and numbers to avoid dealing with the human issues.
2. Society has been deprived of a united and universally respected voice -- that of science -- which may have been sufficient to impact on people of different backgrounds and belief systems.

In the West, moral guidance, and the raising of social consciousness is a task relegated to the clergy, and to such among academics as sociologists.

The clergy, on the one hand, have often remained silent on issues, or been effectively silenced by broad disregard. Also, in the area of morality and science, they have been accused of being unqualified to comment on at least half the debate. Therefore, the clergy has had overall little impact in health care.

The various branches of sociology and anthropology, on the other hand, have busied themselves with academic analytical task of attempting to systematically describe their society. They do not view it as their domain, however, to attempt to systematically change society, and certainly do not as a group propound a philosophy of human accountability and responsibility, and certainly do not extoll religious values.

These voids in general guidance have led to health problems of devastating impact, and only a few surveys and statistics are sufficient to reflect the magnitude of the problem.

However, I caution that I do not view such statistics as heralding the "downfall of the West"; this is a song often sung by those who are unaware of the terrific magnitude, and potential of the West in general, and the United States in particular, to change and to correct.

Also, I do not pose a comparison between East and West; we in the East have sufficient problems to occupy ourselves without the need for comparisons, and both East and West have difficulty.

However, I do mean to point out the results of a particular mindset, which allows the human being to take his will as his Lord, and which confuses licence with freedom, and which strips the human of the dignity of responsibility as God's vicegerent.

Thus, we peruse some statistics:

Over the past 20 years, pregnancy out of wedlock has increased from 15% to 51%. This year alone, the United States anticipates 1,1000,000 pregnancies in the teen-age years, 75% of these being unintentional. Of these, 400,000 will be aborted early in pregnancy, while another 100,000 will abort nearing the third trimester.

This teenage pregnancy annually affects 30,000 girls at the age of 14, and 80% of these permanently leave school and never finish their education.

Overall, 70% of these unwed mothers live on public welfare, which is financed by public taxation[1].

In light of this chaos of modern society, we now have that 51% of all in-hospital admissions for teenagers up to 18 years of age are due to sexually related diseases. In fact, the incidence of gonorrhea among teenage girls has increased 400% in the last 20 years[2].

Also, everyday there are in the United States 2,000 new cases of sexually transmitted disease, bringing the current active total to 12 million cases[3].

We can now begin to project both the physical and financial toll which such statistics imply.

As stated, in 1986 there were 1,200,000 cases of teenage pregnancy. Of those who have children, it is estimated that the government spends $100,000.00 on every unwed mother.

Such costs will in all likelihood climb, given that according to Liebert Sparfbin, in his book "The New Window", that the average person watches on television 9,230 acts of explicit or implied sexual intercourse per year, and 81% of these are among unwed partners[4].

And when we shift from the arena of physical or physiological licence to that of medical licence, the statistics speak equally loudly: Here, I wish only to use the example of Acquired Immune Deficiency Syndrome (AIDS) -- I expect that this topic will receive a fuller treatment in this conference.

I wish only to mention three points:

1. This disease is worldwide in extent, and that the differences in rates between societies is partially explained by the accuracy of diagnosis, as well as the openness or courage about admitting the disease, which is found in some societies and not in others. In the United States, in 1986, there were 250,000 reported cases, doubling annually to our present day.
2. Secondly, the disease often affects those who are completely innocent through the medium of blood transfusions.
3. This disease co-exists with drug addiction, with i.v. drug users now one of the main pockets of incidence and spread. As an aside, it is noted that in the United States in 1985 there were 23,000 cases of in-patients for drug addiction, while in New York in 1987 there were 1,266 beds specified for AIDS patients, up 18% from the previous year. One AIDS patient costs society $147,000.00 for in-hospital expenses, while total patient expenses are estimated to be $635.00 per day. The total cost of AIDS in New York is expected to be $400,000,000.00 (four million) in 1988.[5]

AIDS, however, is clearly most closely associated with, and transmitted by, homosexual activity. In 1986, I presented a paper at the Islamic Medical Conference in Karachi on "The Gay Bowel Syndrome". There, I concentrated on other disease complexes, other than AIDS, which are spread in the homosexual community, and which are often spread to innocent bystanders in their food and drink (e.g. amoebic infestations). The statistics on that disease complex are frightening indeed, and have continued to increase alarmingly since my last paper. The precise statistics are published with the paper in that year's proceedings of the Islamic Medical Conference, and I refer those who are interested to that paper[6].

Also, I would call your attention to the paper presented at the first conference on Islamic Medicine in Kuwait in the year 1981 entitled "Islamic solution for modern resistant problems"[7] (A difficult or recalcitrant medical problem -- the islamic solutions to alcoholism in the American Society). This paper refers us to another health problem directly caused by another type of unchecked freedom.

I would like to briefly append two points to the material of that paper:

1. The latest statistics regarding the impact of alcoholism on the innocent citizens
2. The strong correlation between the hazards of the combination of alcoholism and drug addiction -- In the report of The American Medical Society on Alcoholism published in 1987:

"The significant predictors of mortality risk were alcohol consumption changes in pattern of opioid use, age, and marital status. Addicts who were at high risk of dying (a) consumed large amounts of alcohol (over eight ounces a day), (b) had continued drug problems and also consumed alcohol, (c) were over 36 years of age, and (d) were not married. Heavy alcohol consumption was the strongest predictor with the rate of 29.7 per 1,000 in one year, this rate is close to three times as high as those who drank less than four ounces a day[8].

The limited scope of this paper will not allow the exploration of the different problematic areas of licence. I just tried to offer examples to prove a point. We must emphasize that licence cannot be limited to a specific area of life - it is a generalized trend that will include all aspects. We cannot say let there be sexual corruption but prevent drugs, or allow drugs but fight against violence - not only because the cause effect relation between these different deviations, but also because of the fact that all of them are the outproduct of a certain philosophy, the expression of a specific attitude regarding life - that can be summarized in "It is me, who has to enjoy to the maximum, right now and completely regardless of the consequences".

Amidst this mess, it becomes mandatory - that the Muslim physician, from a medical perspective, should carry the task to challenge the pseudo-scientific prevailing patterns, which treat the symptoms not eradicate the disease - and deal with the crust without addresing the core.

It is beyond the scope of this paper to offer specifics about how to carry on this task, however, I'd like to call on my brothers and colleagues to:

1. Consider the issue of the safety and health of the public as our priority, which must occupy the major part of the agendas of our conferences and direct our collective efforts towards the creation of a medical strategy - which is both deep and comprehensive.
2. This strategy should include a plethora of well controlled scientific research which will defy the established superficial and limited trials.

We may hope, then that this will entice people to reconsider and question their philosophies and attitudes - to bring them closer to the Divine mercy and justice

"THOSE WHOM GOD (IN HIM PLAN) WILLETH TO GUIDE - HE OPENETH THEIR BREAST TO ISLAM"

(S.6:V.125)

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AIDS, THE PROBLEM OF CONTEMPORARY WORLD AND A FUTURE ISLAMIC VIEW

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When Acquired Immunodeficiency Syndrome (AIDS) was first recognized as a clinical entity in 1981, it was thought to be present only in the United States of America and particularly among certain population groups - namely homosexuals and intravenous drug abusers. However, this was soon realized not to be the case when the disease was reported from some other countries, in Europe and America, in 1982 and 1983. It has now become a focus for priority attention by politicians, public health workers, the press and the public.

GLOBAL AIDS SITUATION

The AIDS virus was widespread in many countries before scientists were aware of its existence and before the first cases were reported in 1981. Since the first recognition of AIDS, up to the end July 1988 over one hundred eight thousand cases have been reported to WHO from one hundred and thirty-eight (138) countries. Table 1 shows the number of reported cases by continent and year.

The largest number of cases (over 79 000) have been reported from the Americas. Within the Americas the cumulative notified AIDS occurrence is highest in the Caribbean Islands, especially Bermuda and French Guiana where it has exceeded 100/100 000 population. In the USA the largest volume of cases (over 69 000) in the world were reported; the cumulative notified rate of AIDS cases is 28/100 000 population. The United States Public Health Service estimates that by 1991 more than 1/4 of a million cases would have occurred in the USA.

In Africa, 45 countries reported approximately 15 000 cases. There are wide variations in the cumulative rates of occurrence. It is highest in Congo (58/100 000), followed by Burundi, Uganda and Rwanda, where it is more than 10/100 000. The rates in Central African Republic, Kenya, Malawi, Tanzania, Zaire, Zambia and Zimbabwe are between one and 10/100 000.

In Europe, 28 countries reported over 13 000 cases. The rates of occurrence in Eastern Europe are far less than in Western Europe where most countries are considered to be facing an AIDS epidemic. The highest rates of cumulative notified AIDS cases are in Belgium, Denmark, France, Federal Republic of Germany, Italy, Spain and Switzerland.

It must, however, be remembered that:

Available data give the number of cases reported voluntarily by countries and do not accurately reflect the incidence of the disease on a world-wide basis. Some countries report regularly, others report periodically and no reports at all are received from another group of countries. The current estimate is that there have probably

been twice the number reported, i.e. approximately 200 000 cases of AIDS since the beginning of the pandemic.

TABLE 1. REPORTED CASES OF AIDS BY CONTINENT AND YEARS OF OCCURRENCE (SITUATION AS AT END JULY 1988)

Continent	Before 1983	1983	1984	1985	1986	1987	Up to end July 1988	Not known	Total
Africa (45)*	3	14	82	611	3048	8060	2967	1	14786
Americas (40)	1430	3234	6368	11934	18999	26590	10353	0	78908
Asia (22)	2	8	4	28	47	128	47	0	264
Europe (28)	86	215	564	1331	2570	6077	2363	8	13214
Oceania (5)	1	6	45	124	243	375	210	0	1004
TOTAL (140)	1522	3477	7063	14028	24907	41230	15940	9	108176

* Figures between ( ) represent the number of countries reporting one or more cases.

The reported cases are only the tip of an iceberg. Many of those who are now infected but have no symptoms are expected to develop symptoms in the future. Within five years from infection, approximately 25% of infected persons develop AIDS and another 40% develop a condition known as AIDS-Related Complex (ARC). The risk of the remaining 35% getting the disease is not known. Little is known as to why some infected people develop symptoms while others do not. It is believed that certain factors may trigger off progression from infection to AIDS. These include repeated exposure to infection, infection with diseases such as tuberculosis or malaria, which compromise the immune functions, pregnancy and possibly genetic factors.

Infection once acquired is believed to be lifelong. As infection does not result quickly in illness, followed by death or cure, there is an accumulation of infected people. There is considerable uncertainty about the real number of Human Immunodeficiency Virus (HIV)-infected individuals in different countries although this information is an essential requirement for the development of national strategies for prevention and control. Current estimates suggest that there are approximately 5-10 million persons in the world who are thought to be infected and therefore susceptible to HIV-associated health problems; this means 50-100 or more HIV-infected persons for each of the estimated known cases of AIDS.

It has been estimated that, during the next five years, from one to two million new AIDS cases will emerge from people already infected. This would represent more than a tenfold increase in the numbers reported so far. The number of cases expected during 1988 alone may exceed 100 000. If the progress of the pandemic

remains unchecked the number of infected people in the world in the coming years will indeed be frightening and will subsequently increase to unmanageable proportions.

The epidemiological picture of the disease in various parts of the world presents three distinctive patterns:

1. The first pattern is observed in the United States of America, Western Europe, Australia and New Zealand. In these parts of the world, most of the cases have occurred among homosexuals and mostly among males in the 20-49 years age group. The male-to-female ratio ranges from 10:1 to 15:1. Transmission is mostly through homosexual relations. Heterosexual transmission has hitherto been responsible for only a small percentage of cases, but it is now increasing. Transmission due to blood and blood-products, apart from the role of intravenous drug abuse, is of decreasing importance, particularly with the introduction of screening for blood in most of these countries. Perinatal transmission is still of low importance, particularly as sero-prevalence in the community is in the range of 1%, although among homosexuals it may be as high as 50% in certain communities.

2. The second pattern is the one prevailing in East, Central and South Africa. In this part of the world transmission is mostly heterosexual; the male-to-female ratio is 1:1 and perinatal transmission is common. The role of injections may be important, as proper sterilization of syringes and needles is not universally practised and disposable syringes are not widely used. The sero-prevalence rate is high and in some communities, particularly in young adults, it may be as high as 15%. Among prostitutes in certain communities, HIV infection rates have exceeded 80%.

3. The third pattern is the one which is mostly reported in the Middle East, in Asia and in a large number of the Pacific countries. In these parts of the world, the virus appears to have entered recently. Both homosexual and hetero-sexual transmission is occurring. Cases have in general been found among persons who have travelled in, or had contact with people from, endemic areas, and among people who have received transfusion of blood obtained from countries where the disease is prevalent. The occurrence of the disease is increasing but the sero-prevalence is still very low, indicating lower invasion rates in the community.

EPIDEMIOLOGICAL PATTERN OF AIDS IN THE ISLAMIC COUNTRIES AND COUNTRIES OF THE EASTERN MEDITERRANEAN REGION (EMR)

The epidemiological pattern of AIDS and Human Immunodeficiency Virus (HIV) infection in Islamic countries is quite different from that prevailing in the USA and Europe or Africa. This difference relates to several factors; one of them is the fact that the virus was widespread in the USA and some other countries that are now reporting most of the cases, before scientists knew it existed and before the first cases were reported in 1981. Perhaps there were already hundreds of thousands of infected people when the first cases were reported. The viral invasion and spread in the USA and parts of Europe were to a large extent facilitated by the so-called sexual revolution which had started in the 1960s and continued into the 1970s. In this movement, homosexuals were trying to achieve legitimacy and recognition. They went very far in this direction. Numerous clubs for homosexuals were established and in these clubs multiple sex partnerships were very much promoted. The magnitude of this pattern of behaviour can be visualized from an example taken from a study carried out before the advent of AIDS in one of the homosexual populations in the USA. In this study it was reported that 60% of persons who had sexual relations with each other had these relations even before they knew each others' names. This pattern of sexual behaviour permitted the rapid spread of the virus before scientists knew that it existed.

In Islamic countries there is as yet limited evidence of indigenous transmission except in a small number of countries. Most cases have occurred among two main groups:

— People who have received transfusion of blood obtained from countries where the disease is prevalent. This had been responsible for a large proportion of HIV infections, especially as some countries were importing nearly all their blood and blood-product requirements.

— People who have had sexual contact with persons in areas where the infection is prevalent. They include workers living in Europe and nationals who have travelled abroad for holidays.

MODES OF TRANSMISSION

HIV has been isolated from blood, serum and various body fluids including semen, cervicovaginal fluid, breast milk, tears and saliva. However, detailed epidemiological studies throughout the world have mainly implicated blood, semen and cervicovaginal secretions in transmission. The isolation of the virus from a body fluid does not necessarily mean that the fluid is important in transmission. All epidemiological studies have indicated that there are mainly three basic modes of transmission: (1) sexual (2) parenteral and (3) perinatal.

1. Sexual transmission

HIV is fundamentally a sexually transimitted virus which is transmitted by both homosexual and heterosexual intercourse, this mode of transmission being responsible for more than 90% of cases of infection. It must, however, be remembered that there is no risk of sexual transmission if neither party is infected, such as for example among husbands and wives who mutually restricted their sexual relations to themselves; provided of course that neither was infected before marriage, or through another mode of transmission, e.g. blood transfusion. Certain sexual practices and factors increase the risk of infection, e.g. anal intercourse, the number of sex partners, the presence of other sexually transmitted diseases, and sexual contact with prostitutes. Anal intercourse is more serious than vaginal intercourse, particularly for the receptive partner. This is because it frequently results in slight ruptures in the rectal mucosa through which infected lymphocytes and the HIV virus in semen may enter the tissues and bloodstream of the sexual partner. Vaginal intercourse is capable of transmitting the virus from an infected man to a woman, or from an infected woman to a man.

2. Parenteral transmission

Cases of AIDS acquired through transfusion of blood and blood products represent a small but an important proportion of the total number of cases (2-5%).

Parenteral transmission occurs through the transfusion of infected blood or blood products, and by the use of contaminated needles and syringes or other skin-piercing instruments. In studies of single parenteral exposures, the risk of acquiring HIV infection is related to the inoculum. Recipients of a single unit of blood from an infected person have a high risk of acquiring infection (nearly 90%). To date, whole blood, blood cellular components, plasma and clotting factors have been involved in the transmission of HIV infection. No other products prepared from blood (immunoglobulins, albumin and plasma protein fractions) have been implicated.

Transmission via blood and blood products may become a significant problem in those countries that have not yet implemented nation-wide donor- or blood-screening for evidence of infection with HIV.

In countries with high levels of infection, there is apparently an association between AIDS and medical injections, and injections for ritual purposes, especially where disposable syringes and needles are not available and sterilization procedures are not adequate.

3. Maternal/foetal transmission

Perinatal transmission may occur before, during or shortly after birth. Although all three modes have been documented, the relative importance of each has not been defined. The overall risk of HIV transmission from an HIV-infected mother to her infant ranges from 25%–50%. Post-natal transmission has been described in infants exposed to mothers who acquired HIV infection after delivery; breast milk has been suggested as the possible means of transmission in these cases.

The relative importance of the various modes of transmission differs from one continent to another, from one country to another and even within the same country from one group to another. It is also related to the introduction of screening methods for blood and blood products, which reduce the role of these in transmission.

There is still no evidence to suggest that the virus can be transmitted by the respiratory or enteric routes or by casual person-to-person contact, in the household, social, work, or school environments.

There is no evidence to suggest that insects, food, water, toilets, swimming pools, seats, shared eating and drinking utensils or other items such as second-hand clothing or telephones, are involved in transmitting the disease.

The issue of transmission by saliva is of concern to the public, e.g. from using articles of infected persons or during dental work. It is reassuring to note that the rate of isolation of the virus from saliva is very low (1-2%) from infected persons.

To conclude, HIV is not spread casually. HIV spreads as a result of human action which is subject to human control. Through controlling sexual practices, by screening blood before transfusion and by avoiding the re-use or sharing of contaminated needles and syringes, transmission can be considerably reduced.

SOCIOLOGICAL ASPECTS OF AIDS

AIDS has been described on many occasions as less of a medical than a social problem. This is true; because the occurence of AIDS, like other sexually transmitted diseases, is related to a number of social factors, the most important of which are: homosexuality, prostitution and drug absue. It was therefore felt important to briefly address these three aspects in the context of this Region which includes many Islamic countries.

(a) Homosexuality

In this part of the world there is no doubt that homosexuality, although present, is neither tolerated by the community nor is it legally accepted. Furthermore, homosexuals do not enjoy a high social position, economic or political power or high visibility in society as they do in the USA and Europe where, due to their large numbers, they have advocates for their acceptance and their so-called rights.

It is also important to note that the pattern of homosexuality in this part of the world is very different, especially in certain important aspects related to the spread of AIDS. In this Region, persons involved do not usually have multiple sexual partners and, if grouped at all, then the groups are very small.

It must be mentioned, however, that denial of the presence of homosexuality in our communities will not help to stop its rather limited danger in transmitting AIDS in the Region. On the contrary, it is essential to know more about this high-risk behaviour in order to plan the best approach to address and educate those involved, particularly as broad public information programmes are usually not able to produce behavioural changes among homosexuals to significantly reduce the risk of spreading HIV infections.

(b) Prostitution

There is evidence that heterosexual transmission is playing an increasingly important role in the transmission of HIV infection in this part of the world and the involvement of prostitutes is undeniable. They have been shown in some situations to be the link through which infection is reaching the communities.

Prostitution has been in existence throughout human history, in spite of innumerable attempts at suppression, sometimes violent. Prostitution is no longer found only under conditions of poverty and social hopelessness as it was in the past. In most countries of this Region prostitution is illegal. However, no one can ignore that there are non-registered forms of selling sexual favours. The exact volume of such forms of prostitution in the Region is not known; some national authorities, such as security and police, claim to know, although apparently they do very little about it.

It is not only in this Region, but globally, that the volume of prostitution is not known. In countries where it is legal, amateur prostitution is believed to exceed the licensed form by 5 to 10 times.

Efforts to control prostitution meet with many difficulties. In some countries, national authorities have tried to reduce the number of prostitutes by providing those for whom prostitution was the main source of income with alternative means of support. Experience has shown, however, that prostitutes accept the support but continue to practise their trade.

(c) Intravenous drug abuse

Intravenous drug administration is a behaviour which plays an important role in AIDS transmission. In the USA and Europe, from 1 to 3 per thousand of the population use intravenous drugs regularly and another 1-3 per thousand use them occasionally. However, no one knows the magnitude of intravenous drug abuse in this Region; most probably it is much less than in the USA and Europe.

Drug abusers are an isolated group, not easily reached by health authorities because they tend to be persecuted individuals and not responsive to public health education. They also tend to be forced by their drug dependence into theft, violence and prostitution.

It is more easy to suggest than to actually implement efforts to deal with the drug problem in relation to the spread of AIDS. Some people are advocating simple solutions to complex problems, as for example the free distribution of syringes. One cannot believe that this is the solution, however, taking into account that the cost of a syringe and a needle is negligible in relation to that of the drug. People also speak of motivating drug addicts to understand the consequence of risk behaviour and their ethical responsibility, but some social scientists believe that this cannot be done by a group with an *a priori* irrational behaviour such as drug abuse. They question the possibility of "getting through to" addicts by health education messages and, even if this were achieved, they do not expect that it would be successful in the long term. It is only with drug abuse treatment programmes that HIV infection through this method of transmission may be controlled.

TREATMENT

There is no known treatment regimen to restore the immune status of AIDS patients. Patient care essentially involves the treatment of opportunisitic infections. Since the patient's own immune defence is deficient, treatment with chemotherapeutics and antibiotics is often less effective than in otherwise healthy patients.

Major efforts are under way to develop therapeutic modalities for patients with AIDS and AIDS-Related Complex. Research is being carried out in several fields:

Remarkable progress has been made towards the identification of antiviral agents. A double-blind, placebo-controlled clinical study showed that some categories of AIDS patients receiving azidothymidine (AZT) had gained weight and had a sense of well-being. They regained their skin reactivity and had an increase in the circulation of the helper leucocytes. This meant that AZT appeared to prolong the life of these selected AIDS patients. There are, however, side effects including toxicity involving bone marrow, resulting in some cases in severe anaemia and leucopenia.

AZT is now available on the market, but is still extremely expensive. Important trials have started on HIV-infected people using AZT and other drugs to detect if the progression of AIDS can be blocked.

Several other clinical trials are on the way, using other drugs including ribavirin, dideoxycytidine (DDC), rifamycine, cyclosporine A and interferon, and several other drugs which may hold promise.

In general, antiviral agents were reported to inhibit virus replication in patients. However, it was found that the virus reappeared when medication was stopped. Maintenance treatment for extended periods may be required after viral replication ceases.

VACCINE DEVELOPMENT

The search for an effective vaccine is receiving special attention. Modern techniques in molecular biology have enabled scientists to discover very precisely the chemistry of the virus, but understanding its biological reactions within the host — the key to effective intervention in the process of infection - presents special difficulties because of the type of antibodies it produces. Antibodies produced in response to infection with HIV are of the non-neutralizing variety which means that they have no demonstrable effect on the virus but exist side by side. This does not necessarily mean that vaccine-induced antibodies will not destroy the virus, since they may be different from those induced through the natural infection.

The fact that the genetic structure of the virus varies from one strain to another, especially within the envelope, is anticipated to be another obstacle in vaccine preparation. Research workers have recently discovered that a portion of the envelope remains unchanged in all strains and a vaccine inducing antibodies that recognize this portion is a possibility. The use of live or inactivated whole virus vaccines is not encouraged in view of the potential dangers of integration of the nucleic acid into the host cell DNA. Most of the ongoing trials to develop vaccines are through the use of purified viral material free of nucleic acid.

The first approved clinical trial for a candidate AIDS vaccine in the USA is under way at the National Institute of Allergy and Infectious Diseases (NIAID). It is essentially designed to measure the safety of the vaccine based on a modified protein from the AIDS virus, the gp 160 protein that makes up the viral coat and a membrane part. This phase is expected to be completed by end 1988, although NIAID is having difficulty in attracting enough volunteers.

After the development of a vaccine becomes a fact, its testing will be a major problem as an animal model is needed. The second problem will be concerned with exposure to infection.

There will also be other problems; legal and logistic ones as well as problems associated with costs, but the most important is the fact that it could already be too late for vaccination because infection is spreading so rapidly in the world.

PREVENTION OF AIDS: AN ISLAMIC PERSPECTIVE

By his very nature and the God-given blessings of mind and feeling, man is normally inclined to avoid all sources of harm. In seeking to sharpen this natural disposition, religion keeps reminding man to seek

prevention against harm in life and to safeguard himself against torture in the afterlife. Thus, the glorious Qur'an warns man,

"... AND CAST NOT YOURSELVES BY YOUR OWN HANDS INTO DESTRUCTION"

(S.2:V.195)

forbidding him to inflict, of his own volition, harm upon himself.

Admittedly, AIDS is a serious health problem which therapeutic medicine has, so far, failed to overcome. However, adopting a preventive approach may be the way to combat it. Prevention is based on adherence to the right behaviour which stems, in essence, from the benign traditions and habits ingrained in the religious beliefs of the Islamic nation. The spreading of AIDS in the communities which unashamedly indulge in illicit sexual practices, such as homosexuality and prostitution, and drug abuse is a solid evidence of the wisdom of divine religions which prohibit such harmful habits and practices. In the holy Qur'an, God almighty commands the Prophet (ﷺ) to,

"... ENJOIN THE BELIEVERS TO CAST DOWN THEIR EYES AND GUARD THEIR PRIVATE PARTS; THAT IS PURER FOR THEM. GOD IS AWARE OF WHAT THEY DO".

(S.24:V.30)

Speaking of indecency and its harmful consequences, the Prophet (ﷺ) declares:

"wherever indecency spreads amongst people and is openly practised by them, they would be afflicted by plagues and sufferings unknown to their predecessors".

In fact, the appearance of AIDS is a hard evidence of the truth of the prohecy of God's messenger (ﷺ). During the past two decades, indecency has widely spread and been openly practised in the western communities, so much so that official recognised clubs and societies were established and advertised for its practice. With the condition specified in the prophetic Hadith thus met, the consequence was sure to follow, and indeed it did, with the outbreak of AIDS and other sexually transmitted diseases, which the European community itself calls "plague", the very word used by the Prophet (ﷺ) in the above-cited Hadith.

As it has been proved that sexual intercourse is the major mode of AIDS transmission, prevention can be maintained through abstinence from illicit sex, as enjoined by all religions, as well as through stable and secure marriage based on true affection, intimacy and devotion. Indeed marital relation is one of the most sacred and powerful of human relations. It is a holy bond which God Almighty blessed and emphasized that it may endure and blossom for the continuation of the human race and the stability of communities. In the Holy Qur'an God states:

"AND OF HIS SIGNS IS THAT, HE CREATED FOR YOU, OF YOURSELVES, SPOUSES, THAT YOU MIGHT RSPOSE IN THEM, AND HE HAS SET BETWEEN YOU LOVE AND MERCY".

(S.30:V.21)

All religions view the family, as the cornerstone of society, which if good causes the society to be equally good. It is, therefore, a religious duty to preserve it and strengthen its ties. Once it breaks into a family, the AIDS virus dooms it to total destruction. If an adult contracts the disease, he/she will inevitably transmit it to his/her spouse and children, thus casting his/her family to death and destruction, instead of offering it safety and protection from danger, and preserving its life. Whoever exposes himself to the AIDS infection victimizes a family, causes it to lose its bread-winner and its offspring who would be born sick, suffering from a terrible disease that inevitably leads to death. If we contemplate the prophetic Hadith that reads:

"What a great sin it is for man to cause his dependants to perish",

we realize that prevention against AIDS is, in fact, a religious duty, a social obligation and a national commitment. It is meant to maintain man's welfare in life and the hereafter. Falling into acts of disobedience and following illicit lustful whims lead to sickness in life and to infernal suffering in the afterlife.

I wish to reiterate that those who expose themselves to infection are basically adulterers and drug addicts - they shall live to suffer horror, disquietude and fear, as God Almighty has ordained, and shall then be doomed to eternal suffering in the hereafter. Truly, all these deviant societies are trembling of fear and inflicted with horror and worry, an aspect of God's punishment in life heralding the suffering that awaits them in the afterlife. The believers are guided by the grace of God to keep away from indecencies. They are secure and shall not suffer fear and disease. It is the duty of all muslims to prove to the whole world that abiding by the rules of Islam and keeping away from its prohibitions shall save man not only from infernal suffering in the hereafter, but also from the perils of sickness and fear that may be suffered in life.

May God Almighty guide our steps along the path of obedience and shield us against acts of disobedience.

PART THREE

APPLIED RESEARCH

CHAPTER I

PLENARY LECTURE

1. MEDICINAL PLANTS AND DRUGS *(Not available in English).*
   Prof. Dr. M. Al-Dakhakheney
2. DISCUSSIONS *(Not available in English).*

CHAPTER II

APPLIED WORK IN THE ISLAMIC MEDICINE

1. STUDIES ON NEW INDOLE ALKALOIDS FROM MEDICINAL PLANTS
   Prof. Dr. Attaur Rahman and Dr. H. Rahman
2. THE USE OF NATURAL IMMUNE ENHANCERS IN THE TREATMENT OF FAR ADVANCED CANCER *(Not available in English, but its Abstract included).*
   Dr. Ahmed El-Kadi, *et al.*
3. FUNCTIONAL AND BEHAVIOURAL TERATOLOGICAL STUDIES OF A CERTAIN HERBAL FORMULATION IN RATS.
   Prof. Dr. M.M.A. Elmazar, *et al.*
4. PHARMACOLOGICAL BASIS OF THERAPEUTIC ACTION OF A HERBAL FORMULA IN THE TREATMENT OF CHRONIC BRONCHITIS AND ASTHMA
   Prof. Dr. Mohammad Sabir, *et al.*
5. EFFECT OF CERTAIN MEDICINAL PLANTS CLINICALLY USED IN RHEUMATOID ARTHRITIS ON EXPERIMENTALLY INDUCED ULCERS
   Dr. S.K. Nazimuddin, *et al.*
6. ISLAMIC RULES GOVERNING FOOD
   Prof. Dr. M. Abdussalam
7. DISCUSSIONS

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STUDIES ON NEW INDOLE ALKALOIDS FROM MEDICINAL PLANTS

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INTRODUCTION

Continuing investigations carried out on various plants in our laboratories have resulted in the isolation of forty six new and a large number of known alkaloids. Their structures and configurations were determined with the help of modern spectroscopic techniques including 2D NMR (COSY-45, 2D J-resolved, NOESY), spin-spin decoupling, NOE difference measurements, hetero-COSY and ^{13}C-NMR (DEPT and GASPE) experiments[1-5].

(A) *NEW INDOLE ALKALOIDS FROM RHAZYA STRICTA*

Rhazya stricta Decaisne (Apocynaceae)[6] is a small, glabrous, erect, shrub which is widely distributed in Western Asia and abundantly found in Pakistan. It has long been used in the indigenous system of medicine for the treatment of various ailments[5-9]. The anti-cancer activity of some of the indole alkaloids of this plant is also reported[9-12].

The ethanolic extract of *Rhazya stricta* collected from a small village about 90 km from Karachi, was evaporated into gum, and the separation of crude alkaloids on the basis of their differential basicities have resulted in several pH fractions. These fractions were subjected to column and thin-layer chromatography to afford the following new alkaloids.

Aspidospermidose (1)[13]

This new alkaloidal glycoside showed the UV absorptions (MeOH) at 211, 250 and 303 nm, characteristic for the dihydroindole chromophore. The IR (KBr) spectrum showed intense absorptions at 3400-3450 cm^{-1} (O-H), 1740 cm^{-1} (ketonic C=O), 1650 cm^{-1} (C=C), and 1050 cm^{-1} (C-O).

The high resolution mass spectrum of the alkaloid showed the molecular ion at m/z 442.2444, corresponding to the molecular formula $C_{25}H_{34}N_2O_5$, indicating ten double bond equivalents in the molecule. The peak at m/z 281.1978 ($C_{19}H_{25}N_2$) corresponded to the loss of 161 m.u. ($C_6H_9O_5$, a sugar unit) from the molecular ion while the higly oxygenated fragment at m/z 290.1016 ($C_{15}H_{16}NO_5$) suggested the attachment of the glycosidic linkage with the indole part of the molecule. When the compound was treated with D_2O and the mass spectrum recorded, the M^+ was found to be shifted by 3 m.u., thereby suggesting the presence of three exchangable hydrogen atoms. Linked scan measurements of metastable transitions established that the ion with m/z 290 arose from the ions at m/z 442 and 414 but did not fragment to the ions at m/z 210 and 124, suggesting that m/z 290 is independent of the aspidosperma part of the molecule.

The ^{1}H-NMR ($CDCl_3$, 300 MHz) spectrum showed a three-proton triplet at δ0.62 for the C-18 methyl protons. The C-19 protons appeared at δ1.54 and 0.89 as a multiplet, indicating their non-equivalence. The

upfield chemical shift of the C-21 proton (δ2.34) suggested α-stereochemistry. The C-2 proton appeared at δ3.84 as a double doublet, the rather upfield chemical shift suggesting β-stereochemistry. The upfield chemical shift value of the C-12 proton (δ6.50) indicated the presence of an N_a-glycoside linkage. The presence of $C_6H_9O_5$ sugar unit was also evident from the NMR spectrum. The C-1′ proton appeared at δ4.91 as a broad singlet, the chemical shift being consistent with this type of system. The C-5′ proton appeared at δ3.94, its downfield chemical shift reflecting the presence of the carbonyl function α-to this proton.

The ^{13}C-NMR spectrum ($CDCl_3$, 75 MHz), showed the presence of 25 carbon atoms. The multiplicity assignments were made by carrying out GASPE experiments. The C-18 methyl carbon resonated at δ6.84 while the C-19 appeared at δ29.32. The signal at δ66.62 was assigned to C-21, its chemical shift reflecting α-stereochemistry. Carbon-3′ which is attached to OH and carbonyl group resonated at δ80.41. The C-1′ carbon resonated at δ80.61, its chemical shift suggesting the presence of an N-glycoside linkage (rather than an O-glycosidic linkage) to the hetero-aromatic aglycone. The ^{13}C-NMR assignments are shown around structure **1.**

The relative stereochemistry was determined by a series of NOE difference measurements. The two dimensional spectra (2D J-resolved, COSY-45°, NOESY) and ^{13}C-NMR experiments agreed with the proposed structure. On the basis of above data structure **1** was proposed for aspidospermidose.

Bharhingine (2)[14]

This new strychnos-type alkaloid showed the UV spectrum (MeOH) with absorptions at 210, 230, 270, 307 and 327 nm. The IR spectrum ($CHCl_3$) afforded intense absorptions at 1715 cm^{-1} (amide carbonyl) and 2880-2920 cm^{-1} (C-H).

The high resolution mass spectrum afforded the molecular ion at m/z 292.1571, consistent with the molecular formula $C_{19}H_{20}N_2O$, indicating eleven double bond equivalents in the molecule. The peak at m/z 277 suggested the loss of 15 m.u. (methyl) from the molecular ion while the prominent peak at m/z 263 resulted due to the loss of the formyl group.

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz) showed the presence of ethylidene side chain. The C-16 proton resonated at δ4.64 as a multiplet. A doublet at δ8.55 ($J_{9,10}$ = 7.9 Hz) was assigned to the C-9 proton, the downfield chemical shift providing strong indication of the presence of an N-formyl function. The C-12 proton resonated at δ8.08 as a doublet ($J_{12,11}$ = 7.6 Hz). The rather downfield chemical shifts of the C-10, C-11 and C-12 protons are consistent with the presence of an N-formyl function. A singlet at δ8.62 was assigned to the formyl proton, its upfield shift agreeing with the attachment of the formyl group to a nitrogen function.

Two dimensional ^{1}H-NMR measurements (2D J-resolved, COSY 45°) afforded data consistent with the proposed structure **(3)** for bharhingine. The NOE interactions between C-18H and C-21H established 'Z' configuration of the ethylidine side chain. On the basis of above data structuure **2** was proposed for bharhingine.

Bisstrictidine (3)[15]

This new alkaloid was isolated as an amorphous material. Its UV spectrum (MeOH) showed absorption maxima at 223 and 265 nm indicating the presence of an indolenine chromophore. The IR spectrum ($CHCl_3$) showed the absence of carbonyl functionalities.

High resolution mass spectral measurements afforded the molecular ion at m/z 556.3566, leading to the formula $C_{38}H_{44}N_4$, indicating the presence of 19 degress of unsaturation in the molecule. Other important fragments appeared at m/z 525, 281, 208 and 124.

The ^{1}H-NMR spectrum ($CDCl_3$, 300MHz) was found to be fairly complex. A three-proton triplet at δ0.65 ($J_{18,19}$ = 6.9 Hz) was assigned to methyl protons and a quartlet at δ1.70 ($J_{19,18}$ = 6.9 Hz) was assigned to the methylene protons of the ethyl side chain. The aromatic protons resonated in the region between δ7.2-7.6 as complex multiplets. The methylene and methine protons of bisstrictidine resonated as complex overlapping multiplets in the region between δ1.7-3.9. The signals for the ethyl group attached to a saturated carbon appeared at δ0.40 and δ0.96 for the methyl and the methylene protons respectively. The downfield signals at δ0.65 and δ1.72 assigned to methyl and methylene protons of ethyl group and suggested a double bond between C-20 and C-21 and both C-20 and C-21 are quaternary carbons.

The ^{13}C-NMR spectrum ($CDCl_3$, 75 MHz) showed several interesting features. Out of 38 carbons only 19 carbon signals were observed in the spectrum. This indicated that the alkaloid has a symmetrical dimeric structure. A downfield signal at δ192.20 was assigned to the C-2, α-to the indolenine nitrogen. A signal at δ78.70 was assigned to the C-16 methine carbon atom. Two down-field signals were observed for the carbons α-to the N_b nitrogen, resonating at δ51.40 and δ55.12 which were assigned to C-3 and C-5 methylene carbons respectively. The ^{13}C-NMR shift assignments are presented around structure **3.**

On the basis of above spectral data structure **3** was assigned to the alkaloid, named "bisstrictidine".

Didemethoxycarbonyltetrahydrosecamine (DDCTHS) (4)[16]

The UV spectrum (MeOH) of this new alkaloid was characteristic of the indole chromophore with maxima at 224, 284 and 290 nm. The IR spectrum ($CHCl_3$) exhibited bands at 3500 cm^{-1} (N-H), 2880 cm^{-1} (C-H), but did not show peaks in the carbonyl region.

The high resolution mass spectrum showed a weak molecular ion peak at m/z 564. The most prominent feature of the mass spectrum was a very strong base peak at m/z 126, characteristic of the tetrahydrosecamine system containing a saturated 3-ethyl piperidine ring. Accurate mass measurements of the M^+ peak could not be achieved with an EI source. However, a strong MH^+ signal could be recorded using FAB mass and accurate mass measurements using KI as an internal standard afforded the exact mass to be 564.4141 ($C_{38}H_{52}N_4$). This showed the presence of 15 double bond equivalents in the molecule. The mass spectrum indicated that postsecamidine contained two indole units to which two C_9H_8N units are attached.

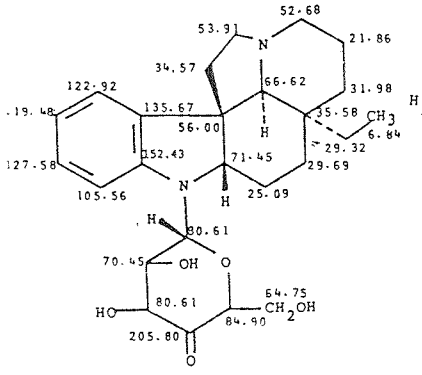
The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz) showed the presence of a six-proton triplet centred at δ0.69 (J = 7.3 Hz) which was assigned to the methyl protons and a four-proton multiplet centred at δ1.16 was assigned to the methylene protons of the ethyl group. The use of spin-spin decoupling as well as 2D-NMR (COSY-45) established the coupling between these.

The ^{1}H-NMR and mass spectroscopic data as well as biogenetic rational agrees with structure **(4)** assigned to DDCTHS. On the basis of these spectroscopic studies structure **4** was proposed for didemethoxycarbonyltetrahydrosecamine.

17′-Hydroxyrhazisidine (5)[17]

This new alkaloid gave a pink colour reaction with ceric sulphate solution. Its UV spectrum showed absorptions at 222, 282 and 290 nm, characteristic for indoles. The high resolution mass spectrum afforded the molecular ion at m/z 632.3750 corresponding to the molecular formula $C_{40}H_{48}N_4O_3$ indicating nineteen degrees of unsaturation in the molecule.

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz) showed the presence of a six proton triplet at δ0.89 (J = 7.0 Hz) for the C-18′ methyl protons. A four proton distorted quartet occurring at δ1.67 were assigned to the C-19 and



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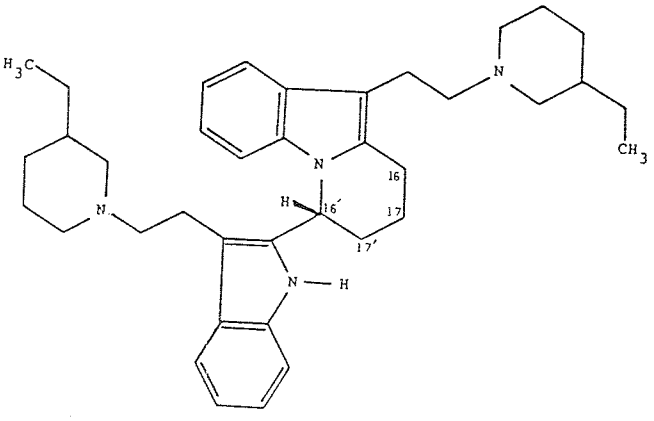

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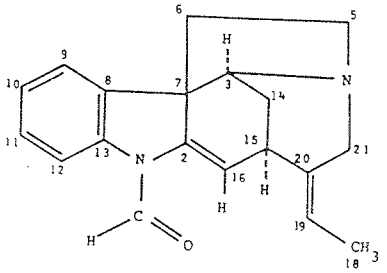

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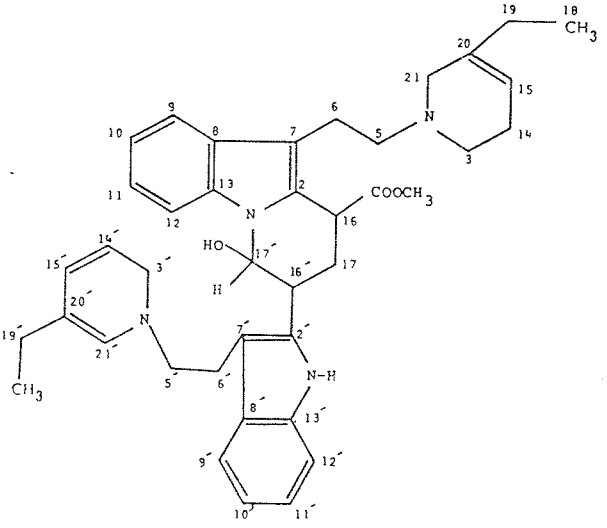

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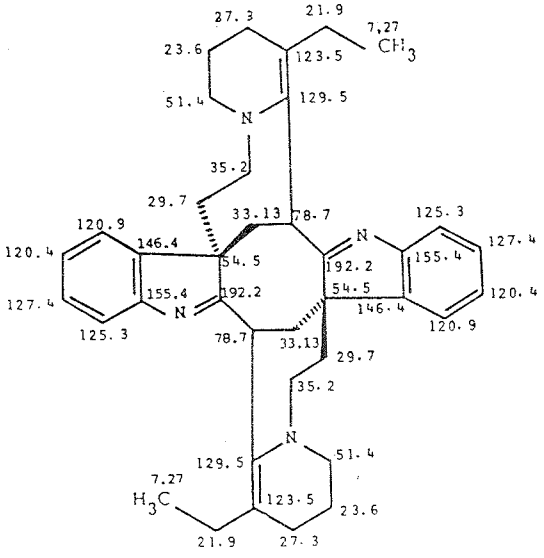

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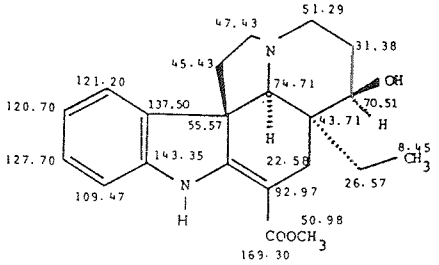

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C-19′ protons. A three proton singlet at δ3.58 indicated the presence of the ester methyl group. A one-proton downfield doublet at δ5.34 ($J_{15,14}$ = 5.5 Hz) was assigned to the C-14 olefinic proton. Complex multiplets in the region between δ7.10-7.70 were assigned to the aromatic protons in the molecule. A one proton singlet at δ7.80 was assigned to the N-H proton.

15-β-Hydroxyvincadifformine (6)[18]

The UV spectrum (MeOH) of this new compound showed absorptions at 205, 224, 296 and 327 nm, indicating the anilinoacrylate chromophore. The IR spectrum ($CHCl_3$) indicated the presence of an ester carbonyl. The high resolution mass spectrum afforded the molecular ion peak at m/z 354.1943 corresponding to the formula $C_{21}H_{26}N_2O_3$, indicating eleven double bond equivalents in the molecule. The peak at m/z 323, ($C_{20}H_{23}N_2O_2$) corresponded to the loss of 31 m.u. (OCH_3) from the molecular ion. Other prominent peaks occurred at m/z 253, 222, 210, 180, 140 and 124. The fragment ions at m/z 210 and 124 are a common feature of Aspidosperma alkaloids.

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz) indicated the presence of ethyl side chain, since it showed a triplet at δ0.67 ($J_{18,19}$ = 7.5 Hz) for the C-18 methyl while the C-19 α and β protons appeared at δ0.96 and δ1.11, showing their non-equivalence. The C-15 proton resonated at δ3.74 as a multiplet, indicating the presence of an oxygen function at this carbon. The singlet at δ3.96 was assigned to the C-21 proton, its downfield shift indicating the α-stereochemistry for this proton. The ester methyl appeared at δ3.75, while the indolic NH appeared at δ8.93. The ^{1}H-^{1}H couplings were established by carrying out two-dimensional NMR (COSY 45, 2D J-resolved) experiments.

Leepacine (7)[19]

This new alkaloid showed UV (MeOH) absorptions at 207, 250 and 298 nm, characteristic for the dihydroindole chromophore. The IR spectrum ($CHCl_3$) of the substance showed intense absorptions at 3350 cm^{-1} (N-H), 1735 cm^{-1} (ester C=O), 1720 cm^{-1} (ketone = C=O), 1605 cm^{-1} (C=C) and 750 cm^{-1} (aromatic C-H).

The high resolution mass spectrum of the alkaloid showed the molecular ion peak at m/z 350.1619, corresponding to the molecular formula $C_{21}H_{22}N_2O_3$, indicating twelve double bond equivalents in the molecule. The peak at m/z 322.1601 ($C_{20}H_{22}N_2O_2$) indicated the loss of 28 m.u. (M-CO) commonly observed in ajmaline type alkaloids. The peak at m/z 292.1575 ($C_{19}H_{20}N_2O$) indicated the loss of ester group as 58 m.u., while the peak at m/z 263 suggested the loss of CHO from m/z 292.

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz) of leepacine showed a three proton doublet at δ1.59 for the methyl group of the ethylidine side chain showing vicinal coupling with an adjacent olefinic proton ($J_{18,19}$ = 6.9 Hz). The C-19 olefinic proton on the other hand resonated as a quartet at δ5.70 showing vicinal coupling with the C-18 methyl protons ($J_{19,18}$ = 6.9 Hz). The C-3 proton resonated as a doublet of double doublets at δ3.24 ($J_{3,14}$ = 10.0 Hz, $J_{3,14} \sim$ 1Hz, $J_{3,2} <$ 1Hz), its upfield chemical shift suggesting α-stereochemistry. The low value of the coupling constants of the C-3 proton with the C-14 proton as well as with the C-2 proton also suggested α-configuration of the proton at C-3. A broad singlet at δ3.95 was assigned to the C-2 proton. This must be in β-configuration since the band with of the signal was found to be characteristically low (<1Hz). The low value of this coupling constant is an account of the dihederal angle between C-2H and C-3H being close to 90°. The ^{13}C-NMR assignments are presented around structure **7.**

Two dimensional NMR (2D J-resolved, COSY-45), NOE difference measurements and ^{13}C-NMR experiments were carried out to verify the assignments. The NOE interactions between the C-15 and C-18

protons, indicated that the 19,20-double bond is in an 'E'-configuration. The NOE difference measurements also served to establish the β and α stereochemistry for the C-2 and C-3 protons respectively.

N_b-Methyl Strictamine (8)[20]

The UV spectrum (MeOH) of this new alkaloid exhibited a characteristic indolenine absorptions at 222 and 265 nm. The IR spectrum ($CHCl_3$) showed an strong absorption at 1740 cm^{-1} indicating the presence of an ester group in the molecule.

The high resolution mass spectrum afforded the molecular ion at m/z 337.1932 corresponding to the molecular formula $C_{21}H_{25}N_2O_2$, representing eleven degrees of unsaturation in the molecule. Other important fragments were present at m/z 322, 308 and 263. The mass fragmentation pattern was found to be very similar to that of strictamine[21].

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz) showed a three proton doublet at δ1.56 ($J_{18,19}$ = 6.9 Hz) for the ethylidine methyl protons. The C-19 olefinic proton appeared at δ5.89 ($J_{19,18}$ = 6.9 Hz) as a quartet. The downfield chemical shifts for the C-3, C-5 and C-21 protons are due to the N^+ function α-to them. The ester methyl protons resonated at δ3.68 as a singlet while the N^+-methyl protons appeared at δ3.80. The presence of four proton signals in the aromatic region suggested the presence of an unsubstituted indolenine nucleus.

The ^{1}H-^{1}H coupling was confirmed by the COSY-45 spectrum while the multiplicities of proton signal were determined by 2D J-resolved spectrum. NOE difference measurements were carried out to confirm the stereochemistry at the asymmetric centres which established 'E' configuration of 19,20 double bond and 'R' configuration at C-16. The ^{13}C-NMR assignments are presented around structure **8.**

Rhazigine (9)[22]

This new alkaloid showed UV (MeOH) absorptions at 225, 282, 290 and 329 nm. The IR ($CHCl_3$) spectrum indicated the presence of an ester group by absorption at 1730 cm^{-1}.

High resolution mass spectral studies afforded the molecular ion peak at m/z 618.3987 corresponding to the molecular formula $C_{40}H_{50}N_4O_2$, indicating 18 double bond equivalents in the molecule. Other prominent peaks appeared at m/z 617, 616, 588, 335, 251 and 124.

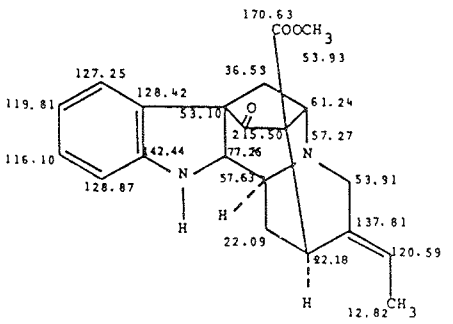
The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz) showed complex overlapping signals. A three proton triplet at δ0.90 ($J_{18,19}$ = 6.2 Hz) was assigned to the methyl protons of ethyl group. A multiplet at δ1.88 was assigned to the C-19 methylene protons of the ethyl side chain. A three proton triplet at δ0.66 ($J_{18',19'}$ = 7.4 Hz) was assigned to the C-18′ protons of the ethyl group. A two proton multiplet at δ2.02 was assigned to the C-19′ methylene protons. The ester methyl protons resonated at δ3.68. A downfield signal at δ7.80 was assigned to the indolic N-H proton. The signal for the C-12 proton was observed at δ7.46 as a doublet ($J_{12',12'}$ = 7.3 Hz). Other aromatic protons resonated as complex multiplets in region between δ6.90 - δ7.30. A one proton distorted doublet observed at δ5.34 (J = 5.3 Hz) was assigned to the C-15′ olefinic proton while another distorted doublet resonating at δ5.59 (J = 8.0 Hz) was assigned to the C-15 olefinic proton.

On the basis of above spectroscopic studies the structure **9** was assigned to rhazigine.

Rhazimine (10)[23,24]

This new alkaloid showed UV (MeOH) absorptions at 222, 265 and 290 nm. The IR spectrum showed absorptions at 1740 cm^{-1} (keto C=O), 1720 cm^{-1} (ester C=O) and 1630 cm^{-1} (C=C).

High resolution mass spectrum afforded the molecular ion peak at m/z 350.1619, corresponded to the



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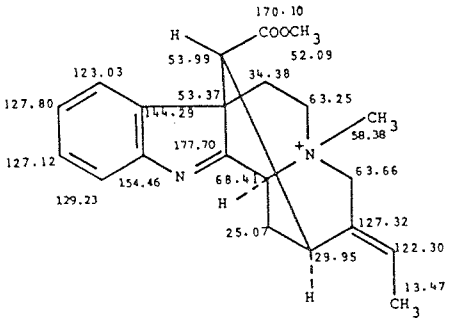

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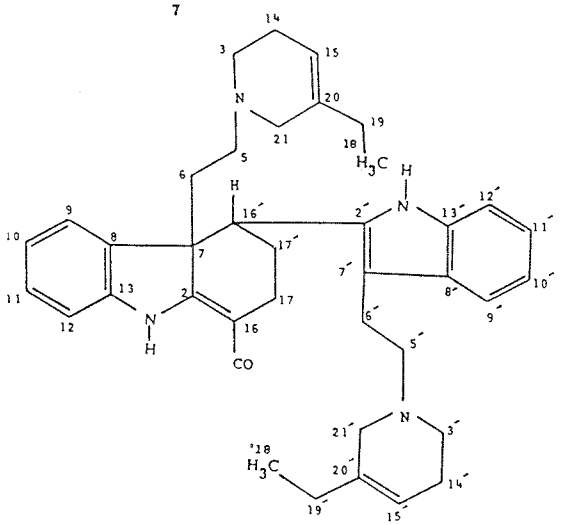

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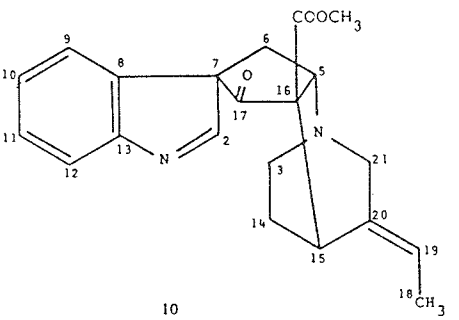

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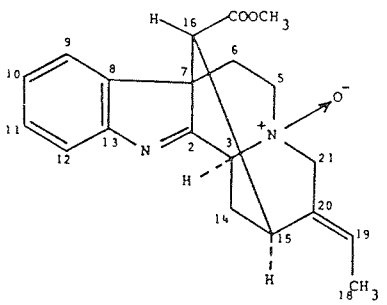

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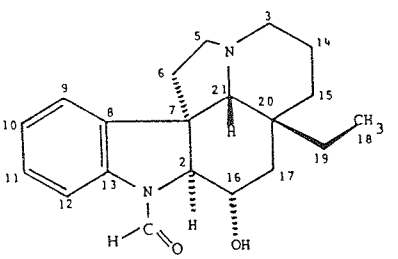

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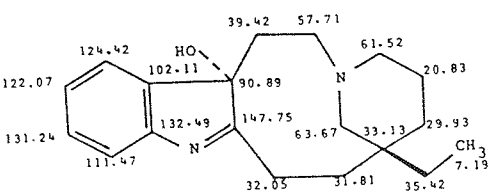
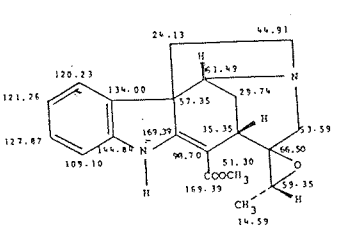


13

molecular formula $C_{21}H_{22}N_2O_3$ indicating the presence of twelve double bond equivalents in the molecule. Other fragments were present at m/z 322.1668 ($C_{20}H_{22}N_2O_2$), 214.0864 ($C_{13}H_{12}NO_2$), 182.0603 ($C_{12}H_8NO$), 167.0738 ($C_{12}H_9N$) and 122.0967 ($C_8H_{12}N$).

The ^{1}H-NMR ($CDCl_3$, 300 MHz) spectrum showed a three proton double doublets at δ1.58 was assigned to the ethylidine methyl group showing vicinal coupling ($J_{18,19}$ = 7.0 Hz) with the adjacent C-19 olefinic proton and homoallylic coupling ($J_{18,21}$ = 2.2 Hz) with the C-21 protons. The C-19 olefinic proton appeared at δ5.57 ($J_{19,18}$ = 7.0 Hz) showing vicinal coupling with the C-18 methyl protons. A three proton singlet at δ3.51 was assigned to the ester methyl. A low field singlet at δ7.70 was of particular significance, its position being in agreement with that expected for an olefinic proton attached to a ketimine carbon.

On the basis of these data structure **10** was originally proposed for rhazimine[23], but in the light of X-ray studies[24] the rhazimine was shown to have structure **10A.** The ^{13}C-NMR assignments are presented around structure **10A.**



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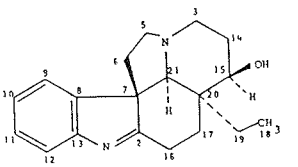

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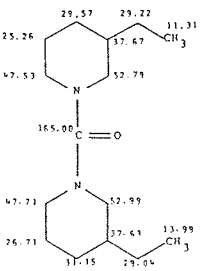

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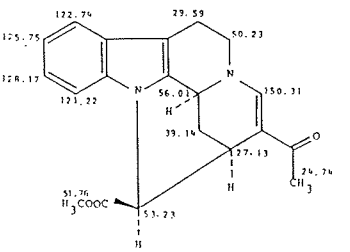

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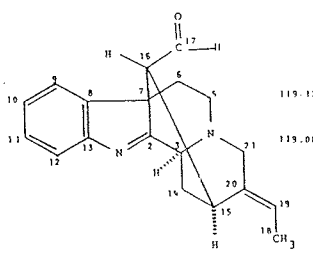

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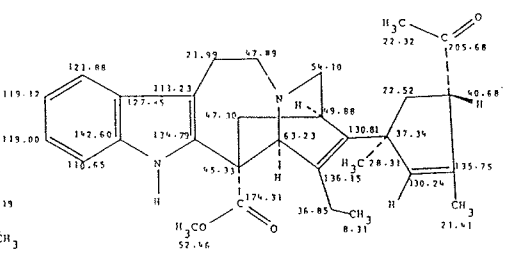

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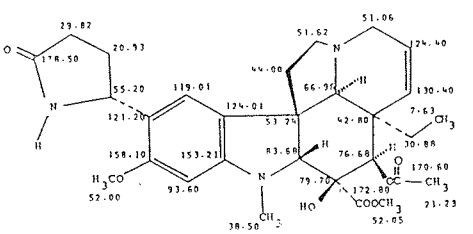

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Strictamine N-oxide (11)[25]

The UV spectrum (MeOH) of this alkaloid showed absorptions at 213 and 262 nm, indicating the indolenine chromophore. The IR spectrum ($CHCl_3$) showed the presence of an ester carbonyl group at 1740 cm^{-1}.

The high resolution mass spectrum afforded the molecular ion peak at m/z 338.1625, which corresponded to the formula $C_{20}H_{22}N_2O_3$, indicating eleven double bond equivalents in the molecule. The mass fragmentation pattern of alkaloid is very similar to that reported for strictamine[21].

The ^{1}H-NMR ($CDCl_3$, 300 MHz) spectrum showed a three proton double doublet at δ1.62 ($J_{18,19}$ = 7.0 Hz, $J_{18,21}$ = 2.5 Hz) assigned to the methyl of an ethylidine group showing vicinal coupling with the adjacent C-19 proton and homoallylic couplings with the C-21 protons. A one proton quartet at δ5.75 ($J_{19,18}$ = 7.0 Hz) was assigned to the C-19 olefinic proton showing vicinal coupling with the C-18 methyl protons. A doublet at δ 2.15 ($J_{16,15}$ = 3.2 Hz) was assigned to the C-16 proton, the upfield shift being on account of the shielding influence of the indolenine nucleus on which it overlies. A characteristic one-proton doublet for the C-3 proton appeared at the rather-downfield position at δ5.61 ($J_{3,14}$ = 6.2 Hz) on account of the deshielding influence of the vicinal quaternary nitrogen. The ester methyl protons appeared at δ3.73.

Because of the strong similarities of the ^{1}H-NMR and the mass spectrum with those of strictamine[21], as well as the polar nature of the compound it was suspected that the substance isolated was strictamine-N-oxide. This was confirmed by deoxygenation in dichloromethane with PCl_3 to strictamine, and by comparison of its spectral data with that reported in the literature.

Strictanine (12)[26]

This new alkaloid showed UV spectrum (MeOH) characteristic for a dihydroindole chromophore with maxima at 212, 253, 280 and 290 nm. The IR spectrum ($CHCl_3$) showed intense absorptions at 3450 cm^{-1} (O-H), 2900 cm^{-1} (C-H), 1680 cm^{-1} (C=O), 1590 cm^{-1} (C=C) and 750 cm^{-1} (aromatic CH).

The high resolution mass spectrum showed the molecular ion peak at m/z 326.1975 leading to the molecular formula $C_{20}H_{26}N_2O_2$, indicating nine double bond equivalents in the molecule. A fragment which occurred at m/z 309.1685 ($C_{20}H_{25}N_2O$) corresponded to the loss of hydroxyl group. The peak at m/z 297 indicated the loss of two different fragments, (i) m/z 297.1954 ($C_{19}H_{25}N_2O$) M^+-CHO and (ii) m/z 297.1647 ($C_{18}H_{21}N_2O_2$) M^+-C_2H_5. This clearly indicated the presence of an aldehydic group as well as an ethyl group.

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz) clearly indicated the presence of N-formyl group : the doublet for C-12H was shifted significantly downfield to δ8.03 in comparison to other aromatic protons. This was indicative of the presence of a carbonyl group at the nitrogen of the dihydroindole nucleus. The presence of four proton signals in the aromatic region indicated a non-substituted benzene ring. The aldehydic proton appeared at δ8.50, its upfield chemical shift suggestive of an N-formyl function. A poorly resolved doublet at δ4.05 (J = 7.0 Hz) may be attributed to the C-2 proton, indicating the substitution of hydroxyl group at C-16. The singlet appearing at δ2.46 was assigned to the C-21H in β-stereochemistry, as earlier been observed in other closely related Aspidosperma alkaloids. On the basis of the above spectroscopic evidences the structure **(12)** was assigned to strictanine.

Strictanol (13)[14,26]

This new alkaloid showed UV (MeOH) absorptions at 227 and 290 nm, indicating the β-hydroxy indoline chromophore. Its IR (KBr) spectrum showed intense absorption at 2970-2860 cm^{-1} (C-H) and 758 cm^{-1} (aromatic C-H).

The high resolution mass spectrum afforded M^+ at m/z 298.2031, leading to the molecular formula, $C_{19}H_{26}N_2O$, indicating eight double bond equivalents in the molecule. The base peak occurred at m/z 281.2021 ($C_{19}H_{25}N_2$), indicating the loss of hydroxyl group. The presence of a prominent fragment at m/z 269.1712 ($C_{21}H_{21}N_2O$), resulting from the loss of the ethyl group from the molecular ion is a common feature of Aspidosperma alkaloids.

The ^{1}H-NMR spectrum (CD_3OD, 300 MHz) indicated the presence of 26 protons. The methyl protons of the ethyl side chain appeared as a triplet at δ0.93 ($J_{18,19}$ = 7.6 Hz). The adjacent methylenic protons (C-19H) resonated as a quartlet as δ1.38 ($J_{19,18}$ = 7.6 Hz). The C-21α proton appeared at δ3.13 as a doublet ($J_{21\alpha,21\beta}$ = 12.2 Hz), while the C-21β proton resonated at δ3.62 ($J_{21\beta,21\alpha}$ = 12.2 Hz). The C-3α proton appeared at δ3.39 as a doublet ($J_{3\alpha,14}$ = 8.1 Hz) while another doublet at δ3.71 ($J_{3\beta,14}$ = 8.1 Hz) was assigned to the C-3β proton. The downfield chemical shift of C-3 and C-21 protons are on account of the adjacent electron-withdrawing nitrogen function. The ^{13}C-NMR assignments are presented around structure **13.**

The structure and stereochemistry of strictanol **(13)** has been investigated by extensive NMR studies (2D J-resolved, COSY-45, NOESY), ^{13}C-NMR, hetero-COSY experiments and NOE difference measurements.

Stricticine (14)[27]

The UV spectrum (MeOH) of this alkaloid gave absorptions at 208, 228, 292 and 327 nm, characteristic of the anilinoacrylate chromophore. The IR spectrum ($CHCl_3$) showed absorptions at 3400 cm^{-1} (N-H) and 1690 cm^{-1} (ester carbonyl).

The high resolution mass spectrum afforded M^+ at m/z 338.1615 in agreement with the formula $C_{20}H_{22}N_2O_3$, indicated eleven double bond equivalents in the molecule. Other prominent peaks occurred at m/z 293, 269, 254, 235, 223, 208, 194 and 180.

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz) indicated the presence of twenty two protons. The coupling interactions between coupled protons were confirmed by spin decoupling experiments and from the COSY-45 spectrum. An upfield three proton doublet at δ0.99 ($J_{18,19}$ = 5.5 Hz) was assigned to the C-18 methyl protons, while a one proton multiplet at δ2.83 was assigned to the C-19 proton. A one proton broad singlet at δ3.62 was assigned to the C-3 proton, its chemical shift suggesting β-stereochemistry. The indole N-H appeared at δ 8.76. The ^{13}C-NMR assignments are presented on structure **14.**

The stereochemistry at the various asymmetric centre was established by carrying out NOE difference studies. This established that the epoxide bearing carbons C-19 and C-20 possessed 'S' configuration. These NOE results also established that the C-18 methyl group overlying the cyclohexane ring system possesses a *cis* configuration.

Strictimidine (15)[28]

The UV spectrum (MeOH) of this new compound showed absorption at 210, 222 and 263, indicating the indolenine chromophore. The IR spectrum ($CHCl_3$) showed no absorption peaks in the carbonyl region but showed intense peaks at 3400 cm^{-1} (O-H), 2900 cm^{-1} (C-H), 1605 cm^{-1} (C=C).

The high resolution mass spectrum indicated the molecular ion peak at m/z 296.1888, corresponding to the molecular formula $C_{19}H_{24}N_2O$, indicating nine double bond equivalents in the molecule. The peak at m/z 279.1602 ($C_{19}H_{23}N_2$) corresponded to the loss of hydroxyl group.

In the ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz) the C-18 methyl protons appeared at δ0.38 as a triplet ($J_{18,19}$ = 7.6 Hz); the C-19α and β protons resonated at δ0.87 and δ1.12 indicating their non-equivalence on account

of their prochiral nature. The C-21 proton appeared at δ2.60 as a broad singlet, its downfield chemical shift suggesting α-stereochemistry. A doublet at δ3.66 ($J_{15,14}$ = 6.7 Hz) was assigned to the C-15 proton having α-stereochemistry, its downfield chemical shift indicating the presence of oxygen function at this carbon.

Strictimine (16)[29]

The UV spectrum (MeOH) of this new alkaloid showed the lack of any chromophoric grouping in the molecule. The IR ($CHCl_3$) showed intense absorptions at 2850 cm^{-1} (C-H) and 1710 cm^{-1} (C=O).

The high resolution mass spectrum afforded the molecular ion at m/z 252.2195, corresponding to the molecular formula $C_{15}H_{28}N_2O$, indicating the presence of three double bond equivalents in the molecule. The mass spectrum indicated that the substance was composed of two ethyl piperidine units. The molecular ion at m/z 252.2195 lost one ethyl group to afford the peak at m/z 233.1805 ($C_{13}H_{23}N_2O$). Alternatively it lost one of the ethyl piperidine units to afford the ion at m/z 140.1080 ($C_8H_{14}NO$) which contained the remaining ethyl piperidine unit and a carbonyl group. The facile loss of C=O from the fragment at m/z 140.1080 ($C_8H_{14}NO$) to afford the ions at m/z 112.1128 ($C_7H_{14}N$) indicated that the carbonyl group was not a part of the piperidine ring but was bonded externally to one of the ring carbon atoms or to the nitrogen. Attempted reduction with sodium borohydride failed to afford the corresponding alcohol indicating that the carbonyl group was not present as a ketone.

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz) showed the presence of a 6-H distorted triplet at δ0.89 (J = 6.5 Hz) which was assigned to the methyl protons of the two ethyl groups. Two downfield multiplets at δ3.52 and δ 3.65 were assigned to the C-2α and β protons. Spin-spin decoupling experiments established that the C-3 and C-3′ methine protons were located as multiplets at δ2.35. The ^{13}C-NMR assignments are shown on structure **16.**

Strictine (17)[30]

The UV spectrum (MeOH) of this new alkaloid showed absorptions at 222 and 295 nm, characteristic for the indole chromophore. The IR spectrum ($CHCl_3$) showed intense absorptions at 1738 cm^{-1} (ketonic C=O), 1670 cm^{-1} (ester C=O) and 1620 cm^{-1} (C=C).

The high resolution mass measurements afforded the molecular ion peak at m/z 336.1462 leading to the molecular formula $C_{20}H_{20}N_2O_3$, indicating twelve double bond equivalents in the molecule.

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz) showed the presence of 20 protons, each of which was identified by a series of homodecoupling experiments and further substantiated by recording COSY-45 spectrum. A three proton singlet at δ2.29 was assigned to the methyl protons of the acetyl group. Another three proton singlet at δ3.57 was consistent with the presence of methyl protons of the carbomethoxy group. A downfield doublet at δ4.60 ($J_{16,15}$ = 4.5 Hz) was assigned to C-16H, which is characteristic for compounds bearing a mavacurine type skeleton[31]. A rather downfield one proton broad singlet at δ7.10 was assigned to the olefinic proton at C-21, its lowfield value being consistent with the presence of an adjacent nitrogen function. The C-3 proton resonated at δ3.60 ($J_{3,14}$ = 6.0 Hz) as a doublet, its chemical shift suggesting α-stereochemistry at C-3. The ^{13}C-NMR assignments are presented on structure **17.**

Strictalamine (18)[32]

The UV spectrum (EtOH) of this new alkaloid showed absorptions at 218 and 265 nm, characteristic of the indolenine chromophore. The IR spectrum ($CDCl_3$) showed the presence of formyl group at 1720 cm^{-1}.

The mass spectrum showed the molecular ion peak at m/z 292.1572 corresponding to the molecular formula $C_{19}H_{20}N_2O$ indicating eleven double bond equivalents in the molecule. Other important peaks appeared at m/z 234, 263 and 264. The peak at m/z 263 suggested the loss of formyl group from the molecular ion. The mass fragmentation pattern was found to be identical with that of strictamine[21].

The ^{1}H-NMR spectrum ($CDCl_3$, 60 MHz) showed the presence of an ethylidine side chain. The methyl of the ethylidine group appeared at δ1.60 as a doublet ($J_{18,19}$ = 7.0 Hz) while the C-19 olefinic proton resonated at δ5.4 as a multiplet. A doublet at δ4.80 was assigned to the C-16 proton. The downfield chemical shift was ascribed to the deshielding effect of the indolenine nucleus. The formyl proton resonated at δ8.75 as a singlet. The aromatic protons appeared at δ7.10 - 7.80 multiplets. The presence of four protons in the aromatic region suggested the lack of substitution in the indolenine nucleus.

On the basis of the above spectroscopic data structure **18** was proposed for strictalamine. This was also established by reduction of strictamine[21] with lithium aluminium hydride to the alcohol which on oxidation gave a compound identical with strictalamine. This established the structure **18** for strictalamine.

(B) *NEW INDOLE ALKALOIDS FROM CATHARANTHUS ROSEUS*

Catharanthus roseus L.G. Don (Apocynaceae) is one of the most thoroughly investigated plants and it owes its reputation to the presence in it of vinblastine and vincristine, two powerful anticancer alkaloids from its leaves, which find wide use in medicine[33-38]. The work on the alcoholic extract of the leaves has resulted in the isolation and structure elucidation of the following new alkaloids.

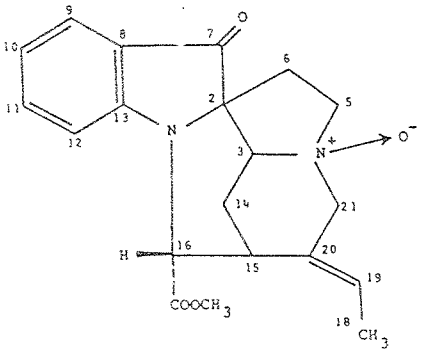
Alioline (19)[39]

A novel alkaloid was isolated from the leaves of *Catharanthus roseus*. Its UV spectrum (MeOH) was typical of indoles with absorptions at 227, 283 and 292 nm. The IR spectrum ($CHCl_3$) showed intense absorptions at 3130 cm^{-1} (N-H), 2910 cm^{-1} (C-H), 1720 cm^{-1} (ester C=O), 1680 cm^{-1} (ketonic C=O), 1600 cm^{-1} (C=C) and 750 cm^{-1} (aromatic C-H).

The HRMS showed the molecular ion at m/z 472.2720 consistent with the molecular formula $C_{30}H_{36}N_2O_3$, indicating fourteen double bond equivalents in the molecule. The peak at m/z 335.1773 ($C_{21}H_{23}N_2O_2$) corresponding to the loss of 137 m.u. ($C_9H_{13}O$) from the molecular ion, established the substitution at C-15. The molecule was seen to be cleaved to afford a peak at m/z 271.1916 ($C_{18}H_{25}NO$) containing the five-membered ring moiety, while the ion at m/z 201.0723 ($C_{12}H_{11}NO_2$) comprised the indolic portion of the molecule.

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz) showed a three-proton triplet at δ0.27 ($J_{18,19}$ = 7.4 Hz). Its rather upfield chemical shift is attributed to its falling in the shielding zone of olefinic bond in the five membered ring. A broad singlet at δ2.58 was assigned to the C-21 proton, its upfield chemical shift suggesting α-stereochemistry. A three-proton singlet at δ3.78 was assigned to the ester methyl protons while two other singlets at δ1.45 and δ1.80 were assigned to the C-4′ methyl and the acetyl methyl on the five-membered ring respectively. The C-1′ methyl appeared at δ0.66 as a singlet, its upfield chemical shift being consistent with the shielding influence of carbonyl function at C-3′. A one-proton singlet at δ5.37 was assigned to the C-5′ proton. The presence of four protons in the aromatic region suggested the lack of substitution of the indole chromophore. The indolic NH resonated as a singlet at δ8.55.

The spin-spin coupling interactions were established through the COSY-45 spectrum while the multiplicity of the overlapping proton signals were determined from the 2D J-resolved spectrum. The NOESY spectrum served to establish spatial proximities while NOE difference measurements confirmed the relative



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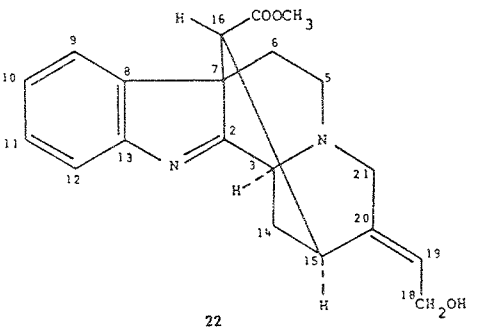

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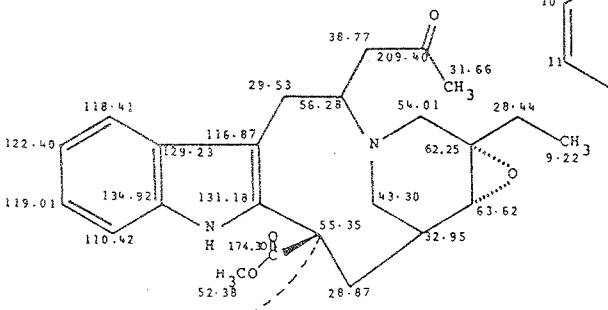

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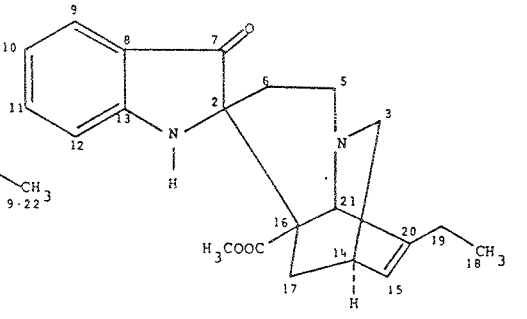

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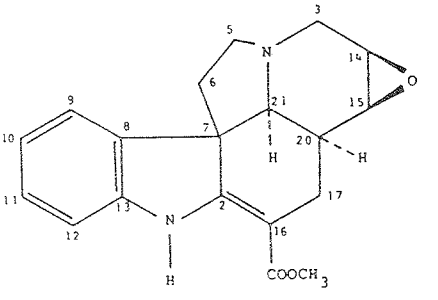

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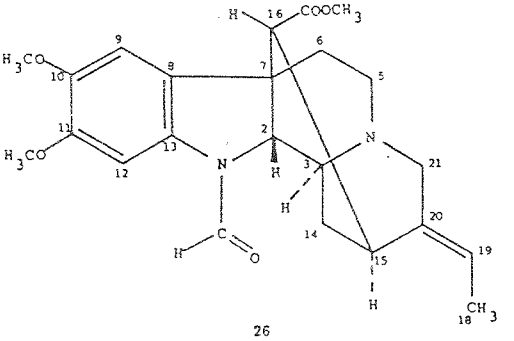

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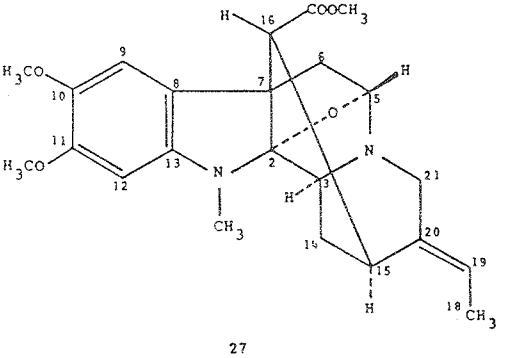

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stereochemistry at various asymmetric centres. The ^{13}C-NMR spectrum ($CDCl_3$, 75 MHz) showed the presence of thirty carbn atoms. The multiplicity assignments were made by DEPT experiments, and the assignments confirmed by carrying out hetero-COSY experiments. On the basis of above data structure **19** was proposed for alioline. The ^{13}C-NMR assignments are presented on structure **19.**

Bannucine (20)[40]

The UV spectrum (MeOH) of this new alkaloid showed absorptions at 238 and 280 nm, showing a slight bathochromic shift from the normal dihydroindole chromophore. The IR spectrum ($CHCl_3$) showed absorptions at 3400 (N-H), 3200 (O-H), 1710 (ester C=O) and 1690 cm^{-1} (amidic C=O).

The HRMS showed molecular ion peak at m/z 539.2612 which was consistent with the formula $C_{29}H_{37}N_3O_7$, indicating thirteen double bond equivalents in the molecule, differing from vindoline by 83 m.u. (C_4H_5NO). The fragment at m/z 84.0449, suggested the presence of C_4H_6NO unit in the molecule. Linked scan measurements were also carried out to determine the fragmentation pathway.

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz) of bannucine showed two 3H singlets at δ3.83 and δ2.07 which were assigned to the methoxy carbonyl and acetoxy methyl groups respectively. The OCH_3 group on the aromatic ring resonated as a 3H singlet at δ3.79, while the N-CH_3 protons appeared as another 3H singlet at δ2.65. The methyl protons of ethyl side chain appeared as a triplet at δ0.44 ($J_{18,19}$ = 7.3 Hz). A doublet at δ5.20 ($J_{15,14}$ = 10.3 Hz) was assigned to the C-15 olefinic proton while the C-14 olefinic proton resonated at δ5.82. Examination of the aromatic region of bannucine showed that only two aromatic protons were present at δ6.08 and δ6.90 each resonating as a sharp singlet. The position of these resonances as well as the lack of *ortho* and *meta* coupling agreed with their being assigned to the C-9 and C-12 protons respectively, indicating that the lactam substituent was attached to C-10. The protons of the five-membered lactam ring substituent at C-10 were readily recognized in the ^{1}H-NMR spectrum.

Two-dimensional NMR measurments (COSY-45, 2D J-resolved, NOESY) fully agreed with the proposed structure **20** for bannucine. The NOESY spectrum established the relative stereochemistry of several key functionalities in bannucine.

The ^{13}C-NMR spectrum is also consistent with the proposed structure **20.** The ^{13}C-NMR shift assignments are presented around structure **20.**

In view of the above data, structure **20** was assigned to bannucine. It is the first aspidosperma alkaloid bearing a five-membered lactam substituent.

Fluorocarpamine-N-oxide (21)[41]

The UV spectrum (MeOH) of this new alkaloid showed absorptions at 235, 257 and 298 nm, characteristic of dihydroindole chromophore. The IR spectrum ($CHCl_3$) afforded absorptions at 1740 cm^{-1} (ester C=O), a- 1685 cm^{-1} (ketonic C=O).

The HRMS afforded molecular ion peak at m/z 354, with characteristic loss of oxygen as encountered in N-oxides. Other major peaks were present at 338, 279, 265, 231, 193, 160 and 121. The fragmentation pattern was remarkably similar to that of fluorocarpamine[42].

The ^{1}H-NMR spectrum ($CDCl_3$, 100 MHz) was similar to that of fluorocarpamine[42]. The substance was treated with PCl_3 in $CHCl_3$. The product was compared with an authentic sample of fluorocarpamine. The polar nature of the material, its characteristic mass spectrum and its readily deoxygenation with PCl_3 to fluorocarpamine unambiguously established it to be fluorocarpamine-N-oxide **(21).**

Gomaline (22)[43]

The UV spectrum (MeOH) of gomaline showed absorptions at 210 and 262 nm, characteristic of the indolenine chromophore. The IR spectrum ($CHCl_3$) showed absorptions at 1725 cm^{-1} (ester C=O) and 3400 cm^{-1} (O-H).

The HRMS bore a distinct resemblance to that of strictamine[21] showing the molecular ion peak at m/z 338.1618, consistent with the molecular formula $C_{20}H_{22}N_2O_3$, indicating eleven double bond equivalents in the molecule. Other major peaks appeared at m/z 321, 279, 261, 232, 206, 180 and 115.

The ^{1}H-NMR spectrum ($CDCl_3$, 100 MHz) showed a one-proton triplet at δ5.57 ($J_{19,18}$ = 7.0 Hz) for an olefinic proton while a two-proton doublet at δ3.94 ($_{18,19}$ = 7.0 Hz) was assigned to the hydroxymethylene protons in an α-disposition. A three-proton singlet at δ3.79 was assigned to the ester methyl group. A doublet at δ4.68 ($J_{3,14}$ = 4.8 Hz) was assigned to the C-3 proton.

The stereochemistry at C-16 emerges from the fact that in the opposite configuration at this centre the proximity with the ketimine group of indolenine system causes an upfield shift of the ester methyl[44]. The stereochemical disposition at C-19 cannot be defined with any certainty, but in view of our earlier establishment of the structure and absolute configuration of the picraline group of bases[45] structure **22** was tentatively proposed for gomaline.

Leurosinone (23)[46]

The UV spectrum (MeOH) of compound **23** showed absorptions at 214, 260 and 296 nm, indicating the presence of both indole and dihydroindole chromophores. The IR spectrum ($CHCl_3$) showed absorptions at 3460 (N-H and O-H) and 1730 cm^{-1} (ester C=O). Interestingly an additional carbonyl absorption was observed at 1710 cm^{-1}.

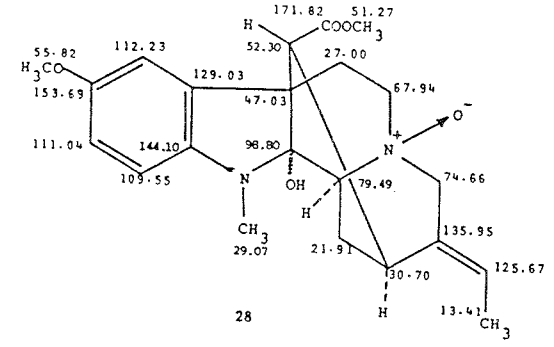
The HRMS showed the molecular ion at m/z 864.4349, corresponding to the molecular formula $C_{49}H_{60}N_4O_{10}$, indicating twenty two degree of unsaturation in the molecule. The overall fragmentation pattern was very similar to that of leurosine[47]. The peak at m/z 208.1327 ($C_{12}H_{18}NO_2$) indicated that the -CH_2COCH_3 unit was attached in the vicinity of the piperidine unit. The possibility of the -CH_2COCH_3 group being present in the vindoline half of the molecule was eliminated from the fact that the normal fragmentation of the vindoline was observed[47].

The ^{1}H-NMR spectrum ($CDCl_3$, 300MHz) showed that a vindoline moiety substituted at the 10-position was present. Two 3H singlets at δ3.78 and δ2.12 were assigned to the methyl groups of the 16-carbomethoxy and 17-acetoxy groups respectively. The 11-OCH_3 group on the aromatic ring resonated as a 3H singlet at δ3.80 while the N-CH_3 protons appeared as another 3H singlet at δ2.70. The ^{1}H-NMR spectrum showed the presence of ethyl side chain and epoxymethine protons. Two striking differences on comparison with the ^{1}H-NMR resonances of leurosinone with that of leurosine, were the presence of an additional 3H singlet at δ2.09 assigned to the methyl of an acetyl group and the absence of the doublet for the 5′β-proton at δ3.67[48], since the -CH_2COCH_3 group was attached at this position in a β-configuration in leurosinone **23.**

A series of NOE difference measurements were carried out to ascertain the position and stereochemistry of the -CH_2COCH_3 group. The ^{13}C-NMR (GASPE and DEPT) experiments supported the structure **23** for leurosinone. The ^{13}C-NMR chemical shift assignments are presented around structure **23.**

Rosamine (24)[49]

The UV spectrum (MeOH) of rosamine showed absorptions at 246, 280 and 340 nm, characteristic of the pseudoindoxyl system. The IR spectrum ($CHCl_3$) showed absorptions at 1720 cm^{-1} (ester C=O) and 1690



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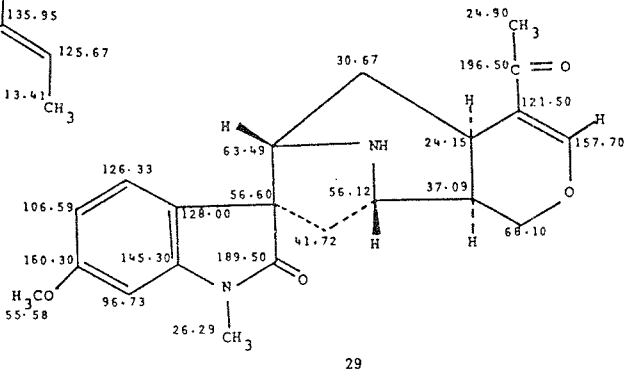

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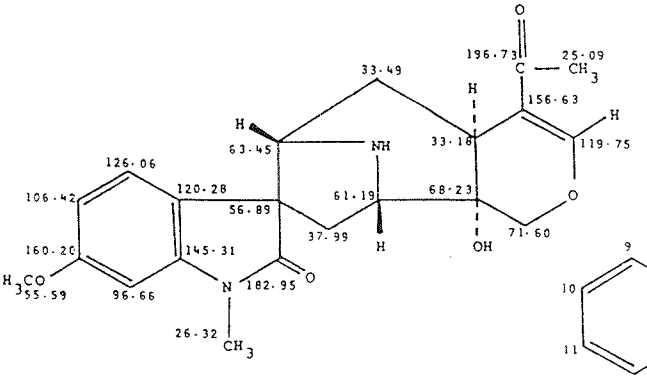

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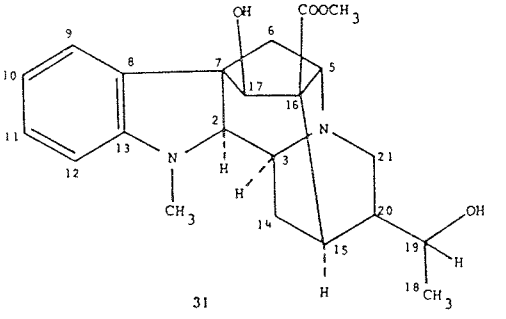

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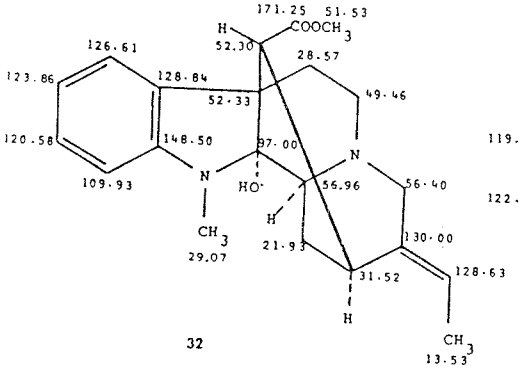

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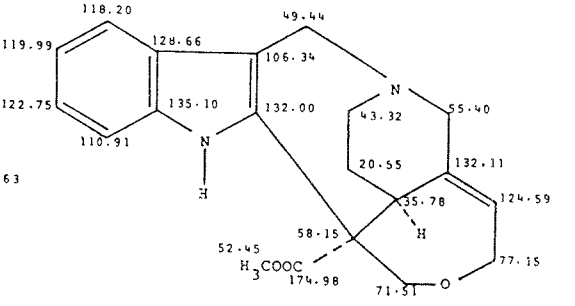

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cm^{-1} (conjugated C=O).

The HRMS showed molecular ion peak at 352.1779, consistent with the formula $C_{21}H_{24}N_2O_3$, indicating eleven double bond equivalents in the molecule. Other major peaks were present at m/z 335, 293, 267, 216, 158, 135 and 107. The peak at m/z 158.0600 ($C_{10}H_8NO$) further suggested the presence of a pseudoindoxyl system.

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz) of rosamine showed a distinct resemblance to the ^{1}H-NMR spectrum of catharanthine[50]. A three-proton triplet appeared at δ1.0 ($J_{18,19}$ = 7.3 Hz) was assigned to methyl group of the ethyl side chain. The ester methyl group resonated at δ3.19, the upfield chemical shift being attributed to the shielding influence of the pseudoindoxyl system.

Rosicine (25)[51]

The UV spectrum (MeOH) of rosicine exhibited aborptions at 203, 223, 295 and 325 nm, characteristic of an anilinoacrylate chromophore. The IR spectrum ($CHCl_3$) showed a strong absorption at 1670 cm^{-1} indicating the presence of an amide or a conjugated ester group.

The HRMS afforded the molecular ion peak at 324.1467, consistent with the formula $C_{19}H_{20}N_2O_3$ indicating the presence of eleven double bond equivalents in the molecule. The mass spectrum showed intense peaks at m/z 214 and 110 often encountered in aspidosperma-type alkaloids bearing an anilinoacrylate skeletal system[52,53].

The ^{1}H-NMR spectrum ($CDCl_3$, 250 MHz) of rosicine was undertaken and the assignments were confirmed by the two dimensional COSY spectrum. A three-proton singlet at δ3.78 was assigned to the ester methyl group. The absence of any other methyl signal indicated that the ethyl or substituted ethyl side chain was absent in rosicine. A low field double-doublet at δ3.38 is assigned to the C-14 proton ($J_{14,3}$ = 5.2 Hz, $J_{14,15}$ = 3.8 Hz). Another lowfield one-proton doublet at δ3.17 is assigned to the C-15 proton. ($J_{15,14}$ = 3.8 Hz). A multiplet at 1.89 was assigned to the C-20 proton. The aromatic protons resonated as complex multiplets in the range of δ6.84-7.28.

The ^{13}C-NMR (GASPE) spectrum supported the structure **25** for rosicine. The ^{13}C-NMR shift assignments are presented in structure **25.**

(C) *NEW INDOLE ALKALOIDS FROM ALSTONIA MACROPHYLLA*

Alstonia macrophylla Wall. is a common plant in Sri Lanka. Several studies on this species growing in other countries have been reported[54-59]. The plant has found wide use in medicinal preparations in the Phillippines[60]. The ethanolc extract of the leaves of *A. macrophylla* of Sri Lankan origin obtained under a joint programme with Sri Lankan scientists afforded the following new alkaloids.

Alstonamide (26)[61]

The UV spectrum (MeOH) of alstonamide showed absorptions at 208, 264 and 300 nm, characteristic for dihydroindole nucleus. The IR spectrum ($CHCl_3$) showed intense absorptions at 2920 cm^{-1} (C-H), 1723 cm^{-1} (ester C=O), 1657 cm^{-1} (N-formyl C=O) and 1600 cm^{-1} (C=C).

The HRMS afforded M^+ at m/z 412.1987, consistent with the molecular formula $C_{23}H_{28}N_2O_5$ indicating eleven degrees of unsaturation in the molecule. The peaks at m/z 383 and 381 suggested the loss of CHO and OCH_3 groups while the peak at m/z 325 corresponded to the loss of ester group from m/z 384.

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz) showed a 3H double doublet at δ1.60 ($J_{18,19}$ = 7.O Hz, $J_{18,15}$ ~

$J_{18,21}$ = 1.8 Hz) for the C-18 methyl. The C-19 olefinic proton resonated at δ5.43 as a split quartet ($J_{19,18}$ = 7.0 Hz, $J_{19,15} \sim J_{19,21} \sim$ 1 Hz). A broad singlet at δ3.72 was assigned to the C-2 proton in its β-configuration. The ester methyl protons resonated at δ3.86 as a singlet while the other 3H singlets at δ3.81 and δ3.82 were assigned to the 10-OCH_3 and 11-OCH_3 protons respectively. Two singlets at δ7.79 and δ7.05 were assigned to the C-9 and C-12 protons. The downfield chemical shifts for the C-9H and C-12H were attributed to the deshielding effect caused by the N-formyl function. The presence of two proton signals in the aromatic region indicated the existence of a disubstituted indole nucleus. A one-proton singlet at δ8.47 was assigned to the N-formyl function.

Two dimensional NMR measurements (COSY-45°, 2D J-resolved) were carried out to verify the assignments. The NOE difference measurements were carried out to establish the stereochemistry at various asymmetric centres. It established 'E' stereochemistry of the ethylidine side chain.

On the basis of the above spectroscopic studies structure **26** was assigned to alstonamide.

Alstopicralamine (27)[62]

The UV spectrum (MeOH) of this new alkaloid showed absorptions at 230, 245 and 300 nm, revealing the presence of a dihydroindole system. The IR spectrum ($CHCl_3$) displayed intense absorptions at 1723 cm^{-1} (ester C=O), 1600 cm^{-1} (C=C) and 1280 cm^{-1} (C-O).

The HRMS afforded molecular ion peak at m/z 412.1813 in agreement with the formula $C_{23}H_{28}N_2O_5$, indicating eleven double bond equivalents in the molecule. The peak at m/z 353 arose by the loss of carbomethoxy group from M^+. A peak at m/z 135 corresponded to the substituted piperidine ion. The fragmentation pattern were distinctly similar to that of other picraline bases.

The ^{1}H-NMR spectrum ($CDCl_3$, 400 MHz) showed a three-proton double doublet at δ1.51 ($J_{18,19}$ = 7.0 Hz, $J_{18,21}$ = 2.4 Hz) assigned to the methyl of the ethylidine side chain while the C-19 olefinic proton appeared at δ5.52 ($J_{19,18}$ = 7.0 Hz) as a quartet. A three-proton singlet at δ2.94 was due to the N-CH_3 proton. The spectrum showed three 3-H singlets at δ3.65, 3.75 and 3.86 corresponding to two methoxy groups and one carbomethoxy group. The ester methy protons appeared at δ3.65 as a singlet. The 2D COSY-45 spectrum confirmed the ^{1}H-^{1}H couplings in the molecule.

On the basis of the above studies, structure **27** was assigned to alstopicralamine.

Alstozine N-oxide (28)[63]

The UV spectrum (MeOH) of this new alkaloid showed absorptions at 212, 245 and 307 nm, characteristic of a dihydroindole chromophore. The IR spectrum ($CHCl_3$) exhibited intense absorptions at 3660 cm^{-1} (O-H), 2900 cm^{-1} (C-H), 1724 cm^{-1} (ester C=O), 1595 cm^{-1} (C=C) and 980 cm^{-1} (C-O).

The HRMS displayed the molecular ion peak at m/z 400.1975 corresponding to the molecular formula $C_{22}H_{28}N_2O_5$, indicating the presence of ten double bond equivalents in the molecule. The peaks at m/z 384 and 383 suggested the loss of oxygen and hydroxyl group from the molecular ion. The overall mass fragmentation pattern was similar to those of picralima alkaloids.

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz) revealed a three-proton double doublet at δ1.47 ($J_{18,19}$ = 7.1 Hz, $J_{18,21}$ = 1.9 Hz) for the C-18 methyl protons. The vicinal vinylic proton appeared as a quartet at δ5.65 ($J_{19,18}$ = 7.1 Hz). A doublet at δ2.74 ($J_{16,15}$ = 4.0 Hz) was assigned to the C-16 bridghead proton. The C-3, C-5 and C-21 protons appeared downfield due to the N^+ function. A 3H singlet at δ2.63 was assigned to the N-CH_3 group while another 3H singlet at δ3.49 was due to the ester methyl protons. The aromatic region showed

three one-proton signals suggesting a mono-substituted dihydroindole nucleus. A 3H singlet at δ3.68 was assigned to the aromatic methoxy protons.

Two dimensional NMR experiments (COSY-45°, 2D J-resolved) were carried out to verify the assignments. The NOE measurements suggested the 'E' stereochemistry of the ethylidine side chain and α-stereochemistry of the hydroxyl group at C-2. The ^{13}C-NMR assignments are presented on sructure **28.**

N_b-Demethylalstophylline oxindole (29)[64]

The UV spectrum (MeOH) of this new alkaloid displayed characteristic absorptions for the oxindole system with absorptions at 223, 256, 286 and 294 nm. The IR spectrum ($CHCl_3$) showed absorptions at 1650 (conj. C=O) and 1705 cm^{-1} (lactam C=O).

The HRMS showed the molecular ion peak at m/z 368.1736, in agreement with the molecular formula $C_{21}H_{24}N_2O_4$, indicating eleven double bond equivalents in the molecule. The peak at m/z 179.0949 resulted from the cleavage of the spiran ring. The accompanying peaks at m/z 161 and 136 are associated with the loss of water and an acyl radical (CH_3CO) from m/z 179. The reto Diels-Alder type fragmentation of the ring D gave rise to the indole-containing fragment at m/z 244.

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz) showed three methyl singlets at δ 2.24, 3.17 and 3.18. These signals were assigned to the acetyl methyl, N_a-methyl and methoxy groups respectively. The rather lowfield value of the N_a-methyl group suggested that the nitrogen bearing methyl group was adjacent to the lactam carbonyl group. The typical pattern of signals at δ6.45, 6.80 and 8.16 confirmed the presence of a methoxy substituent at C-11 of the aromatic nucleus. A low field singlet at δ7.62 was assigned to the C-21 olefinic proton, its downfield chemical shift value is because of it being in the β-position to the carbonyl group and the presence of an adjacent oxygen. The spin-spin coupling interactions were determined through the COSY-45 spectrum while the multiplicities of the proton signals were unambiguously determined by 2D J-resolved spectrum. In order to confirm the relative stereochemistry at various asymmetric centres NOE diference measurements were carried out.

The ^{13}C-NMR spectrum (CDl_3, 75 MHz) showed twenty one carbon resonances. The multiplicity assignments were made by using DEPT experiments. These experiments revealed the presence of three methyl, three methylene and eight methine carbons in agreement with structure **29.** The ^{13}C-NMR assignments are presented on structure **29.**

On the basis of the above spectroscopic data, structure **29** was assigned to N_b-demethylastophylline oxindole.

16-Hydroxy-N_b-demethylalstophylline (30)[65]

The UV spectrum (MeOH) of 16-hydroxy-N_b-demethylalstophylline oxindole afforded absorptions at 218, 215, 235, 285 and 294 nm, characteristic of oxindole alkaloids. The IR spectrum ($CHCl_3$) showed absorptions at 1690 cm^{-1} (lactam C=O) and 1620 cm^{-1} (α,β-usaturated C=O).

The HRMS showed the molecular ion peak at m/z 384.1672 corresponding to the formula $C_{21}H_{24}N_2O_5$ indicating the presence of eleven double bond equivalents in the molecule. The peak at m/z 354.1603 ($C_{20}H_{22}N_2O_4$) suggested the loss of CH_2O from the molecule. An important peak appearing at m/z 195.0893 ($C_{10}H_{13}NO_3$) after removal of a water molecule afforded the peak at m/z 177.0765 corresponding to the formula $C_{10}H_{11}NO_2$. This suggested that there is a hydroxyl group at C-16 in the molecule.

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz) showed three methyl singlets at δ2.23, 3.14 and 3.82. These signals were assigned to the acetyl methyl, N_a-methyl and methoxy methyl protons, respectively. The rather

lowfield value of N_a-methyl protons suggested that the nitrogen bearing methyl group was adjacent to the lactam carbonyl group. The typical pattern of signals at δ6.42, 6.77 and 8.05 confirmed the presence of a substituent (OMe) at C-11 of the aromatic nucleus. The NOE experiments served to establish the β-stereochemistry of proton at C-3 and C-5. It also established the α-stereochemistry of proton and hydroxyl group at C-11 and C-16 respectively.

On the basis of the above spectroscopic data, structure **30** was assigned to 16-hydroxy-N_b-demethylalstophylline.

δ6.42, 6.77 and 8.05 confirmed the presence of a substituent (OMe) at C-11 of the aromatic nucleus. The NOE experiments served to establish the β-stereochemistry of proton at C-3 and C-5. It also established the α-stereochemistry of proton and hydroxyl group at C-11 and C-16 respectively.

On the basis of the above spectroscopic data, structure **30** was assigned to 16-hydroxy-N_b-demethylalstophylline.

19-Hydroxyvincamajine (31)[66]

The UV spectrum (MeOH) of this new alkaloid showed absorptions at 175 and 247 nm. The IR spectrum ($CHCl_3$) contained a carbonyl at 1730 cm^{-1}, and a band at 740 cm^{-1}, characteristic of an *ortho*-disubstituted benzene.

The HRMS showed the molecular ion peak at m/z 384.2036 corresponding to molecular formula $C_{22}H_{28}N_2O_4$, indicating twelve degrees of unsaturation in the molecule. The ^{1}H-NMR spectrum showed a close resemblance to that of vincamajine[67], except for the doublet at δ1.0 which was assigned to the C-19 methyl group.

On the basis of the above spectroscopic data, structure **31** was assigned to 19-hydroxyvincamajine.

Strictaminolamine (32)[68]

The UV spectrum (MeOH) of strictaminolamine was characteristic of the dihydroindole chromophore with absorptions at 207, 244 and 292 nm. The IR spectrum ($CHCl_3$) displayed strong absorptions at 1720 cm^{-1} (ester C=O) and 1595 cm^{-1} (C=C).

The HRMS showed the molecular ion peak at m/z 354.1947 corresponding to the molecular formula $C_{21}H_{26}N_2O_3$, indicating the presence of ten double bond equivalents in the molecule. The mass spectrum of the compound after deuterium exchange with CD_3OD showed an increase of one m.u. in M^+ confirming the presence of one exchangeable proton (OH group).

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz) showed a three-proton double doublet at δ1.45 ($J_{18,19}$ = 7.2 Hz, $J_{18,21}$ = 1.9 Hz) which was assigned to the methyl group of the ethylidine side chain. The C-19 olefinic proton appeared as a split quartet at δ5.42 ($J_{19,18}$ = 7.2, $J_{19,15} \sim J_{19,21}$ = 1Hz). Two singlets at δ2.69 and 3.51 were assigned to the N-CH_3 and carbomethoxy methyl protons respectively. The aromatic region showed the presence of four signals each integrating for one-proton, corresponding to the four aromatic protons of the dihydroindole nucleus.

Two dimensional NMR experiments (COSY-45, NOESY) were carried out to verify the assignments. The NOESY spectrum established the relative stereochemistry at various asymmetric centres and suggested the "E" configuration for the 19,20 double bond. The ^{13}C-chemical shifts are presented around structure **32.**

On the basis of the above spectroscopic studies, structure **32** was assigned to strictaminolamine.

(D) *NEW INDOLE ALKALOIDS FROM ALSTONIA SCHOLARIS*

Alstonia scholaris (Apocynaceae) locally known as "chaliyum" is a large evergreen tree. The extract of the plant has been used in the indigenous system of medicine for the treatment of various diseases[69,70]. The alcoholic extract of the stem bark showed anti-cancer activity in HS_1 human sarcoma[71,72] and also exhibited significant antimicrobial activity[73]. The ethanolic extract of the leaves of *A. scholaris* has afforded the following new alkaloids.

Alstonamine (33)[74]

The UV spectrum (MeOH) of alstonamine showed absorptions at 222, 283 and 290 nm, characteristic of the indole chromophore. The IR spectrum ($CHCl_3$) showed absorptions at 3300 cm^{-1} (N-H) and 1725 cm^{-1} (ester C=O).

The HRMS showed the molecular ion peak at m/z 338.1632, corresponding to the molecular formula $C_{20}H_{22}N_2O_3$, indicating eleven double bond equivalents in the molecule. Other significant peaks were observed at m/z 307, 251, 206, 157, 170 and 122.

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz) was very similar to that reported for vallesamine[75]. The main difference was the absence of signals for the methyl protons and the presence of two double doublets centered at δ4.50 ($J_{18\alpha,18\beta}$ = 14.2 Hz, $J_{18\alpha,19}$ = 5.4 Hz) and at δ4.21 ($J_{18\beta,18\alpha}$ = 14.2 Hz, $J_{18\beta,19}$ = 3.4 Hz) which were assigned to the 18 α and β protons respectively. The ester methyl protons resonated as a 3H singlet at δ3.88 while the olefinic proton resonated at δ5.53. The close resemblance of the ^{1}H-NMR signals of alstonamine with those of vallesamine, and the absence of the 18-methyl protons indicated that the C-18 carbon had undergone cyclization with the C-17 hydroxyl group to generate a new 7-membered ring in alstonamine **33.**

In order to confirm the assignments in the ^{1}H-NMR spectrum a comprehensive series of homodecoupling experiments were carried out. The chemical shifts, coupling constants and ^{1}H-^{1}H coupling were confirmed by recording the 2D, COSY-45 and 2D J-resolved spectra. The ^{13}C-NMR assignments are presented around structure **33.**

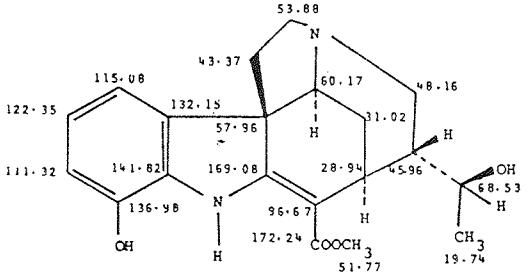
On the basis of above spectroscopic studies structure **33** was assigned to alstonamine.

Scholaricine (34)[76]

The UV spectrum (MeOH) of scholaricine showed absorptions at 210, 235, 285 and 335 nm, characteristic of an anilinoacrylate chromophore. The IR spectrum ($CHCl_3$) gave absorptions at 3500 cm^{-1} (O-H), 3400 cm^{-1} (N-H) and 1660 cm^{-1} (α,β-unsaturated C=O).

The HRMS afforded the molecular ion peak at 356.1736 corresponding to the molecular formula $C_{20}H_{24}N_2O_4$, indicating ten double bond equivalents in the molecule. The peak at m/z 257.1299 ($C_{15}H_{17}N_2O_2$) suggested the loss of 99 m.u., which corresponds to the cleavage of a fragment bearing the conjugated ester group.

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz) showed a three-proton singlet at δ3.83 which is assigned to the ester methyl protons. The 18-methyl protons afforded a doublet at δ1.12 ($J_{18,19}$ = 6.0 Hz) suggesting the presence of O-CH-CH_3 moiety as in scholarine[77]. Integration of the aromatic region showed the presence of only three protons, which indicated the existence of a substituent in the benzene ring. The aromatic protons gave a complex ABC type multiplets in the region δ6.63 to δ7.12. This suggested that the OH group was present at C-9 or C-12, as location of the OH group at C-10 or C-11 would have afforded a readily recognizable AB pattern. The ^{13}C-NMR assignments are presented around structure **34.**



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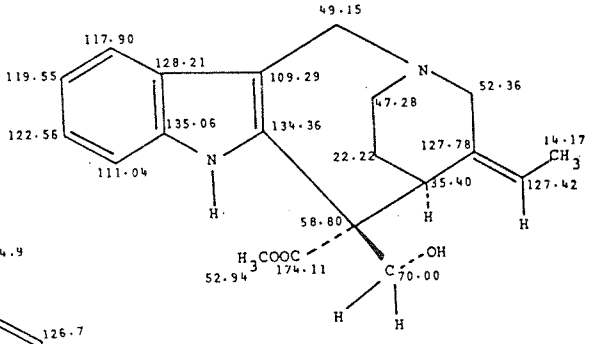

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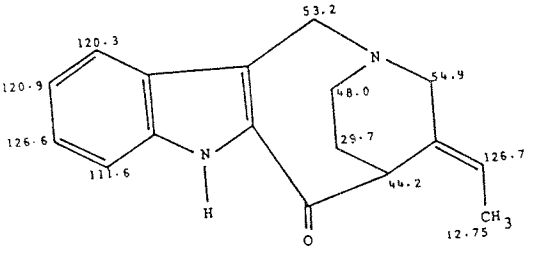

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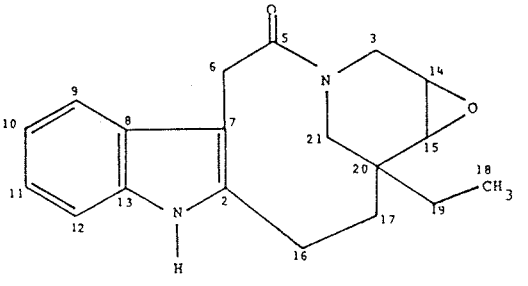

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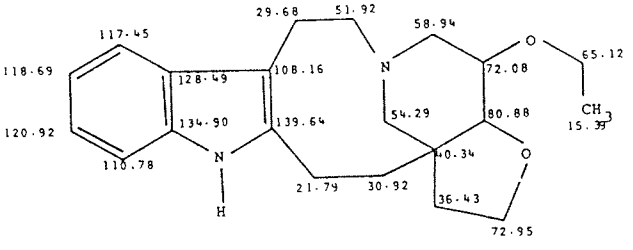

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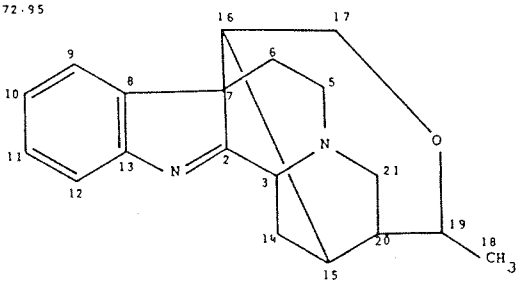

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On the basis of above spectroscopic studies structure **34** was assigned to scholaricine.

19,20-Z-Vallesamine (35)[78]

The UV spectrum (MeOH) of this new alkaloid was found to be characteristic for the indole chromophore, showing absorptions at 225, 275, 282 and 293 nm. The IR spectrum ($CHCl_3$) showed absorptions at 3300 cm^{-1} (N-H) and 1725 cm^{-1} (ester C=O).

The HRMS showed the molecular ion at m/z 340.1947, corresponding to the molecular formula $C_{20}H_{24}N_2O_3$, indicating ten double bond equivalents in the molecule. Other significant peaks were observed at m/z 208, 143 and 122. The mass fragmentation pattern was identical to that reported for vallesamine[75].

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz) showed a doublet at δ1.69 ($J_{18,19}$ = 6.4 Hz) for the ethylidine methyl group while the C-19 olefinic proton resonated at δ5.52 as a quartet ($J_{19,18}$ = 6.4 Hz). The ester methyl protons appeared at δ3.70 as a singlet. The C-6α and β protons appeared as a doublet each at δ4.93 and δ4.05 (J = 16.4 Hz), the downfield chemical shift reflecting the α-nitrogen function.

The ^{13}C-NMR spectrum ($CDCl_3$, 75 MHz) showed 20 carbon resonaces. The multiplicity of each carbon atom was determined by using DEPT experiments. The experiments revealed the presence of one methyl carbon, five methylene carbons and six methine carbons, in agreement with structure **35.** The chemical shifts of 19,20-Z-vallesamine were similar to those reported in the literature for vallesamine[75]. The major difference appeared at C-19 and C-20 carbons which were shifted by 3.32 ppm downfield and δ4.62 ppm upfield respectively, thereby indicating a change in the stereochemistry at the 19,20 double bond. The ^{13}C-NMR shifts are presented around structure **35.** The nOe difference measurements also showed that the 19,20 double bond has "Z" configuration.

On the basis of the above spectral studies, structure **35** was assigned to the substance (19,20-Z-vallesamine).

(E) *NEW INDOLE ALKALOIDS FROM ERVATAMIA CORONARIA*

Ervatamia coronaria Stapf. is widely distributed in tropical countries as a garden plant. The plant has found wide use in the indigenous system of medicine for the treatment of various diseases[79]. The alkaloids from the plant caused temporary leukopenia in rats [80]. The ethanolic extract of the dried leaves of *Ervatamia coronaria* have afforded the following new indole alkaloids.

Ervaticine (36)[81]

The UV spectrum (MeOH) of this new alkaloid showed absorptions at 235 and 312 nm, indicating the presence of a 2-acyl indole chromophore. The IR spectrum (KBr) indicated the presence of a carbonyl group at 1640 cm^{-1}. The HRMS afforded molecular ion peak at m/z 266.1412 corresponding to the molecular formula $C_{17}H_{18}N_2O$, indicating ten double bond equivalents in the molecule. Linked scan measurements of the metastable transitions were also carried out to verify the ion fragmentation pathway.

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz) of ervaticine was strikingly similar to that of vallesamine[75]. The C-18 methyl group appeared as a doublet at δ1.52 ($J_{18,19}$ = 6.9 Hz), while the C-19 olefinic proton resonated at δ5.49 ($J_{19,18}$ = 6.9 Hz). A doublet observed at δ3.98 ($J_{15,14}$ = 6.0 Hz) was assigned to the C-15 proton. The downfield shift for the C-15 proton was accounted for by the presence of the adjacent carbonyl group. The NH proton resonated as a broad singlet at δ8.92. The pattern of protons in the aromatic region was typical of an unsubstituted indole ring.

All these assignments and inter-relationships were confirmed by homonuclear decoupling as well as by 2D J-resolved and 2D NMR (COSY-45) experiments.

The ^{13}C-NMR spectrum ($CDCl_3$, 75 MHz) showed various diagnostic carbon chemical shifts. The C-18 methyl carbon appeared at δ12.75. The signal at δ44.2 was assigned to C-15 which was located at the α-position of the carbonyl group. The signal due to the C-19 olefinic carbon atom appeared at δ126.70.

The presence of the 2-acyl indole moiety was confirmed by the reduction of ervaticine with sodium borohydride in methanol. The stereochemistry at some key centres of ervaticine was established by carrying out nOe difference measurements. These served to establish "Z" configuration of ethylidine side chain.

In the light of above spectroscopic evidences structure **36** was assigned to ervaticine.

Ervatinine (37)[82]

This new alkaloid exhibited absorptions at 205, 227 and 300 nm in its U.V. spectrum which were consistent with the presence of the indole nucleus. The IR spectrum ($CHCl_3$) showed absorptions at 3500 cm^{-1} (O-H), 3425 cm^{-1} (N-H), 2920 cm^{-1} (C-H), 1220 cm^{-1} (C-O-C, epoxide) and 1690 cm^{-1} (amide carbonyl group).

The HRMS afforded the molecular ion peak at m/z 326.1626 corresponding to the molecular formula $C_{19}H_{22}N_2O_3$, indicating ten double bond equivalents in the molecule. The peaks at m/z 152.1073 ($C_9H_{14}NO$), 140.1077 ($C_8H_{14}NO$) and 124.0810 ($C_7H_{10}NO$) revealed that the piperidine moiety bears only one oxygen atom. The fragments at m/z 279, 226 and 175 indicated that the carbonyl group of the amide function could be attached to C-5. Attempted reduction with sodium borohydride failed to afford any reduced product, supporting the presence of an epoxide group in the piperidine ring.

The ^{1}H-NMR spectrum ($CDCl_3$, 100 MHz) showed a triplet at δ0.81 ($J_{18,19}$ = 7.0 Hz) for the methyl protons and a quartet at δ1.12 ($J_{19,18}$ = 7.0 Hz) was attributed to the methylene protons of the ethyl group. A doublet at δ2.80 ($J_{15,14}$ = 4.5 Hz) and a multiplet at δ3.20 gave support to the presence of an epoxide group. These signals were assigned to the C-15 and C-14 protons respectively. The NH proton resonated as a broad singlet at δ8.25.

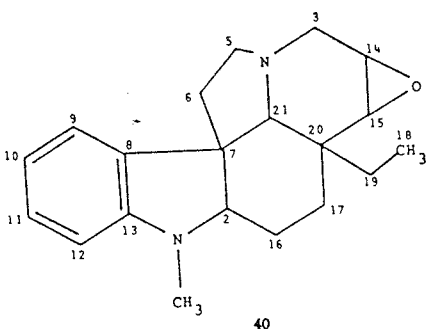
On the basis of these spectroscopic data, structure **37** was assigned to ervatinine.

Hyderabadine (38)[83]

The compound afforded typically indolic UV spectrum (MeOH) showing absorptions at 229 and 284 nm. The IR spectrum ($CHCl_3$) afforded absorptions at 3300 cm^{-1} (N-H) and 2920-2850 cm^{-1} (C-H), but did not show any absorptions in the carbonyl region.

The HRMS afforded the molecular ion peak at m/z 340.2152, consistent with the molecular formula $C_{21}H_{28}N_2O_2$, indicating nine double bond equivalents in the molecule. Other prominent peaks appeared at m/z 311, 295, 265, 225, 183, 182, 157, 156, 152, 144, 143, 110 and 108.

The ^{1}H-NMR spectrum ($CDCl_3$, 100 MHz) showed the presence of a triplet centred at δ1.21 (J = 7.0 Hz) and a quartet centred at δ3.39 (J = 7.0 Hz) which were assigned to the methyl and methylene protons of an ethoxy group. A downfield doublet centred at δ4.52 ($J_{15,14}$ = 7.0 Hz) was assigned to the C-15 proton. A complex multiplet in the region δ3.73-3.93 was ascribed to the oxymethylene protons at the C-18. A broad signal at δ8.25 was assigned to the indolic N-H group. The ^{13}C-NMR shift assignments are presented around structure **38.**



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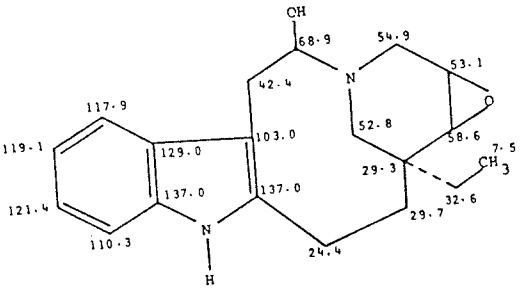

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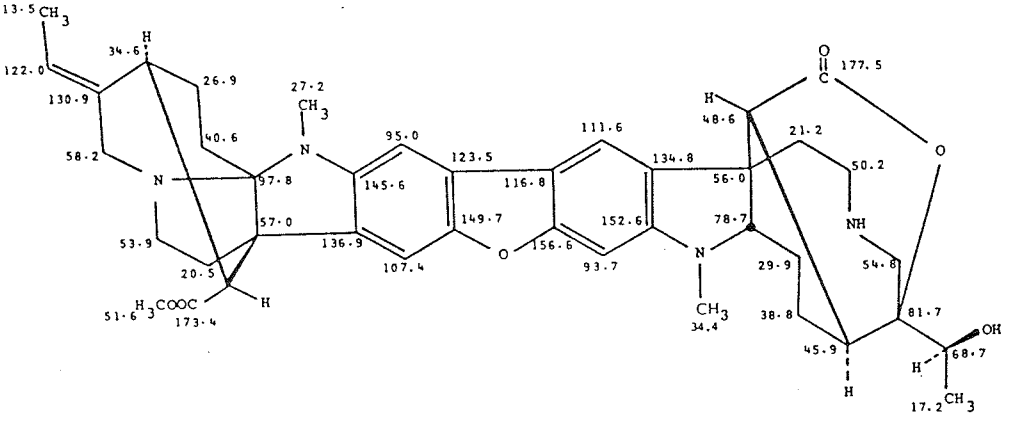

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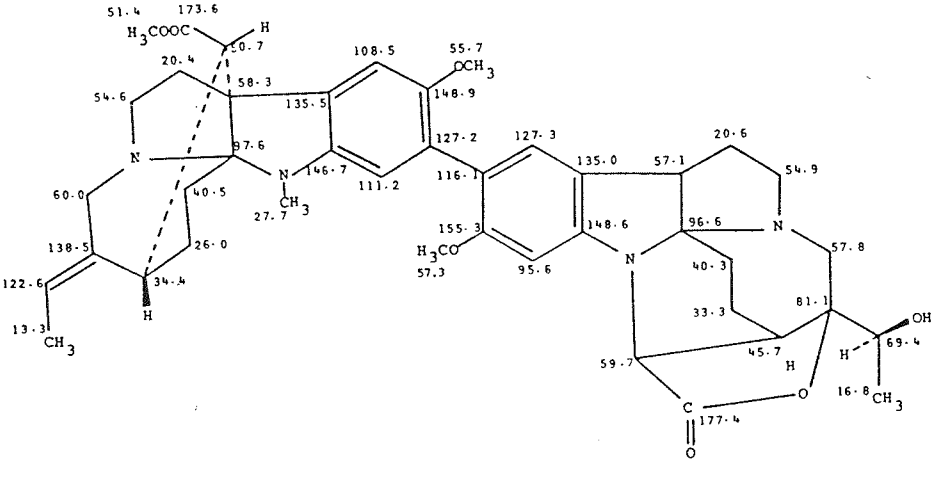

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In consideration of the data presented above structure **38** was proposed for hyderabadine.

Lahoricine (39)[84]

The UV spectrum (MeOH) of this new alkaloid showed absorptions at 220 and 260 nm, indicating the presence of an indolenine chromophore. The IR spectrum ($CHCl_3$) did not show the presence of olefinic or carbonyl groups but indicated the presence of an ether linkage (absorption at 1150 cm^{-1}).

The HRMS showed the molecular ion peak at m/z 294.1719, corresponding to the molecular formula $C_{19}H_{22}N_2O$, indicating ten double bond equivalents in the molecule. The peaks at m/z 279 and 277 were attributed to the loss of methyl and hydroxyl group from the molecular ion respectively. The failure of attempted acetylation supported the presence of the oxygen atom as an ether linkage.

The ^{1}H-NMR spectrum ($CDCl_3$, 100 MHz) showed a three-proton doublet at δ0.93 ($J_{18,19}$ = 7.0 Hz) assigned to the C-18 methyl protons suggesting that it is adjacent to the carbon directly linked to the oxygen atom. The C-19 proton was observed as a multiplet centred at δ3.51. Another downfield multiplet at δ3.17 was assigned to the C-17 methylene protons. A downfield double doublet centred at δ3.87 ($J_{3,14}$ = 3.0 Hz, $J_{3,14'}$ = 8.0 Hz) was attributed to the C-3 proton.

In view of the above spectroscopic studies structure **39** was proposed for lahoricine.

Mehranine (40)[85]

This new alkaloid showed UV spectrum (MeOH) typical of the dihydroindole chromophore, showing absorptions at 209, 257 and 305 nm. The IR spectrum ($CHCl_3$) indicated the presence of N-CH_3 group (2800 cm^{-1}) and an epoxide group (1250 cm^{-1}).

The HRMS showed the molecular ion peak at m/z 310.2056, corresponding to the molecular formula $C_{20}H_{26}N_2O$, indicating nine double bond equivalents in the molecule. Since the IR spectrum did not show any absorptions in the carbonyl region and since attempted acetylation failed to give any acetylated product it, appear plausible that the oxygen atom was present as an epoxide linkage. The fragment ion at m/z 293.2046, attributed to the loss of hydroxyl radical, indicated the presence of an epoxide group in the molecule.

The ^{1}H-NMR spectrum ($CDCl_3$, 100 MHz) showed the presence of a ethyl group since it showed a triplet at δ0.81 ($J_{18,19}$ = 7.0 Hz) for the C-18 methyl protons, while the C-19 methylene protons were observed at δ1.27 ($J_{19,18}$ = 7.0 Hz) as a quartet. A three-proton singlet at δ2.75 indicated the presence of the N-methyl group. A doublet at δ2.96 ($J_{15,14}$ = 4.1 Hz) was assigned to the C-15 proton. The C-2 proton resonated as a double doublet centred at δ3.58 ($J_{2,16\alpha}$ = 12 Hz, $J_{2,16\beta}$ = 6 Hz) while a singlet at δ2.25 was assigned to the C-21 proton. The aromatic protons appeared as a complex multiplet in the region of δ7.00-7.50.

In view of the above spectroscopic studies structure **40** has been proposed for mehranine.

Stapfinine (41)[86]

This new alkaloid afforded a typical UV spectrum (MeOH) showing absorptions at 222, 275 and 292 nm, characteristic for the indole chromophore. The IR spectrum ($CHCl_3$) showed absorptions at 3450 cm^{-1} indicating the presence of a hydroxyl group in the structure. Absorptions at 1460, 1360 and 1240 cm^{-1} were indicative of the presence of an epoxide or ether linkage.

The HRMS showed the molecular ion peak at m/z 312.1821 corresponding to the molecular formula $C_{19}H_{24}N_2O_2$, indicating nine double bond equivalents. The fragment observed at m/z 294.1728 ($C_{19}H_{22}N_2O$) due to the loss of 18 m.u., indicated the presence of a hydroxyl group in the molecule. Similarly, the fragments

at m/z 138.0917 ($C_8H_{12}NO$) and 124.0761 ($C_7H_{10}NO$) demonstrated that only one oxygen atom is present on the piperidine ring.

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz) showed a 3H triplet at δ0.74 ($J_{18,19}$ = 7.4 Hz) and a quartet at δ1.22 ($J_{19,18}$ = 7.4 Hz) for the methyl and methylene protons of the ethyl group respectively. The C-15H resonated as a doublet at δ3.25 ($J_{15,14}$ = 3.0 Hz) and the C-14H appeared at δ2.90 as a multiplet. The rather upfield chemical shifts for the C-14 and C-15 protons indicated that the epoxide possessed a β-configuration[82]. A broad singlet at δ7.73 was assigned to the NH protons. The presence of four proton signals in the aromatic region suggested the lack of substitution on the indole chromophore. These assignments were confirmed by homo-decoupling experiments, 2D NMR (COSY-45, 2D J-resolved) experiements.

The ^{13}C-NMR spectrum ($CDCl_3$, 75 MHz) was also in agreement with the proposed structure **41.** The multiplicity assignments were made by the DEPT pulse sequence. The signal at δ68.90 was assigned to C-5 bearing the OH group. The C-14 and C-15 methine carbons were observed at δ53.10 and δ58.60 respectively. All the other carbons displayed signals at expected values and the ^{13}C-NMR assignments are presented around structure **41.**

On the basis of this spectral data, structure **41** is proposed for stapfinine.

(F) *NEW INDOLE ALKALOIDS FROM PETCHIA CEYLANICA*

Petchia ceylanica Wight is an evergreen herb, indigenous to the lowlands of Sri Lanka. The alcoholic extract of the leaves and stems of *Petchia ceylanica* have resulted in the isolation of the following new alkaloids.

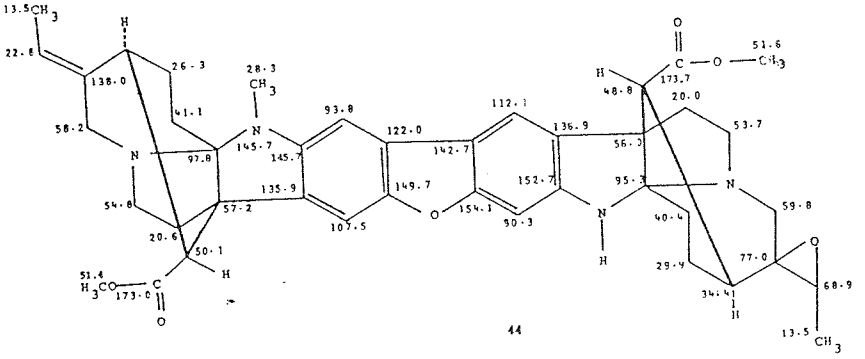
Ceylanicine (42)[87]

This new alkaloid was isolated as a light yellow-coloured amorphous solid from the extracts of the stem of *Petchia ceylanica.* The UV spectrum (MeOH) showed absorptions at 245, 276 and 355 nm, suggesting a dihydroindole skeleton with N-C-N linkage[88]. The IR spectrum (KBr) showed absorption at 3400^{-1} (O-H), 1720 cm^{-1} (ester C=O) and 1765 cm^{-1} (γ-lactone).

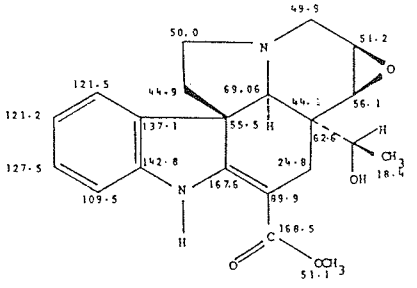
The HRMS showed the molecular ion peak at m/z 692.3499, corresponding to the molecular formula $C_{41}H_{48}N_4O_6$, indicating twenty double bond equivalents in the molecule. Other major peaks appeared at m/z 664, 524, 496 and 495. The mass fragmentation pattern was found to be almost identical to that of desmethylpeceyline[89].

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz) exhibited four 1H singlets at δ7.78, 7.74, 6.71 and 6.65, which were assigned to the aromatic protons at the C-9′, C-12, C-9 and C-12′ respectively. This indicated a similar substitution pattern in ceylanicine as in other dimers isolated from *Petchia ceylanica*[90]. The ethylidine methyl protons appeared as a split double doublet at δ1.65 ($J_{18,19}$ = 6.8 Hz, $J_{18,21\beta}$ = 1.0 Hz), which showed vicinal coupling with the quartet at δ5.41 for C-19H ($J_{19,18}$ = 6.8 Hz). The *E*-stereochemistry of the ethylidine side chain was established by nOe difference measurements. The *R*-configuration of the hydroxy group at C-19′ was established by Horeau's method[91]. The N-methyl singlets appeared at δ2.73 and δ2.61, while a 3H singlet at δ3.78 was assigned to the carbomethoxy methyl protons.

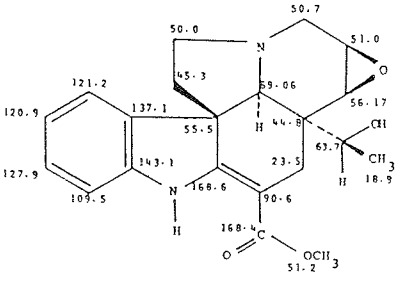
The ^{13}C-NMR spectrum ($CDCl_3$, 75 MHz) indicated the presence of eleven methine, ten methylene, five methyl and thirteen quaternary carbon atoms in addition to an ester carbonyl and γ-lactone carbonyl group. The ^{1}H-NMR and ^{13}C-NMR data indicated the attachment of the two moieties to form the common unsymmetrically substituted dibenzofuran system. A downfield methine at δ78.69 for the C-2′ indicated β-configuration of the proton at this centre[92]. The ^{13}C-NMR shift assignments are presented on structure **42.**



44



45



On the basis of these studies, structure **42** was proposed for ceylanicine.

Ceylanine (43)[87]

This new alkaloid was isolated as a pale-coloured pink amorphous solid. The UV spectrum (MeOH) showed absorptions at 265, 300 and 330 nm. The IR spectrum (KBr) showed absorptions at 3400 cm^{-1} (O-H), 1768 cm^{-1} (C=O of γ-lacton) and 1735 cm^{-1} (ester C=O).

The HRMS showed the molecular ion at m/z 722.3592 corresponding to the formula $C_{42}H_{50}N_4O_7$, indicating twenty double bond equivalents in the molecule. A prominent peak at m/z 694 ($C_{40}H_{46}N_4O_7$), corresponded to the loss of ethylene by a retro Diels-Alder cleavage of the ring D.

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz) showed a 3H singlet for the N-methyl protons at δ2.72, a 3H singlet for the ester methyl protons at δ3.64, two 3H singlets for the six methoxy protons at δ3.72 and δ3.82. The lack of splitting and the chemical shifts of aromatic protons indicated that the substituents were present at the C-10, C-10′, C-11 and C-11′ positions. A three-proton doublet at δ1.59 ($J_{18,19}$ = 6.8 Hz) was assigned to the C-18 methyl while the 3H split doublet at δ1.18. A one-proton split doublet at δ4.68 ($J_{16',15'}$ = 6.0 Hz) was characteristic for the C-16′H. The upfield chemical shift for the C-16′H established it to be β-oriented[93].

The ^{13}C-NMR spectrum ($CDCl_3$, 75 MHz) exhibited eleven methine, ten methylene and six methyl carbons, the multiplicity was established by DEPT experiments. The ^{13}C-NMR shift assignments are shown around structure **43.** The nOe difference measurements established the *E*-stereochemistry of the ethylidine side chain. The *R*-configuration of the hydroxyl group at the C-19′ was established by Horeau's method[91].

On the basis of the above data structure **43** was assigned to ceylanine.

Desmethylpeceyline (44)[89]

A new dimeric indole alkaloid desmethylpeceyline was isolated from the leaves of *Petchia ceylanica.* The UV spectrum (MeOH) showed absorptions at 204, 245, 272 and 347 nm, consistent with the presence of a chromophore comprising an indoline system with another nitrogen atom β to the indoline nitrogen[88]. The IR spectrum ($CHCl_3$) showed absorptions at 3400 cm^{-1} (N-H) and 1738 cm^{-1} (ester C=O).

The HRMS afforded M^+ at m/z 690.3465, corresponding to the formula $C_{41}H_{46}N_4O_6$, indicating twenty one double bond equivalents in the molecule. The mass fragmentation follows a path similar to that of corymine[94].

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz) showed four aromatic proton signals as singlets which appeared at δ6.51, δ6.67, δ7.40 and δ7.41 assigned to C-12′, C-12, C-9 and C-9′ protons respectively, suggesting that there were two aromatic protons in each moiety with a *para* disposition to one another. The C-19 olefinic proton resonated as a quartet at δ5.12 ($J_{19,18}$ = 6.7 Hz). The two 3H singlets at δ3.83 and δ3.84 was assigned to the two methoxy groups. The two C-methyl doublets appeared at δ1.31 ($J_{18',19'}$ = 6.0 Hz) and δ1.69 ($J_{18,19}$ = 6.7 Hz) corresponding to the C-18′ and C-18 methyl protons respectively. The C-19′ oxymethine proton resonated as a quartet at δ3.09 ($J_{19',18'}$ = 6.0 Hz) while the N-methyl protons appeared at δ2.75.

The ^{13}C-NMR spectrum ($CDCl_3$, 75 MHz) showed the presence of the ethylidine, O-methyl and N-methyl groups. The ^{13}C-NMR shift assignments are presented around structure **44.** The nOe difference measurements established that the vinocrine moiety of desmethylpeceyline bears the N-methyl group while the other moiety is demethylvincorine oxide.

On the basis of the above spectroscopic data, structure **44** was assigned to desmethylpeceyline.

(19R)-Epimisiline (45)[91]

The UV spectrum (MeOH) of this new alkaloid was characteristic of an anilinoacrylate chromophore showing absorptions at 328, 297 and 205 nm. The IR spectrum ($CHCl_3$) gave absorptions at 3500 cm^{-1} (O-H), 3350 cm^{-1} (N-H) and 1680 cm^{-1} (α,β-unsaturated C=O).

The HRMS of the alkaloid showed the molecular ion peak at m/z 368.1741, corresponding to the molecular formula $C_{21}H_{24}N_2O_4$, indicating eleven double bond equivalents in the molecule. Its mass fragmentation pattern indicated the presence of an aspidosperma skeleton.

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz) showed a doublet at δ1.15 ($J_{18,19}$ = 7.0 Hz) which was assigned to the C-18 methyl protons, its chemical shift being consistent with the presence of a -CH (OH)CH_3 moiety, or scholaricine[76]. The C-19 methine proton geminal to the hydroxyl group resonated as a multiplet centred at δ3.35. The C-3α proton resonated at δ2.90 as a multiplet while a double doublet at δ3.52 ($J_{3\beta,3\alpha}$ = 12.7 Hz, $J_{3\beta,14\alpha}$ = 5.4 Hz) was assigned to the C-3β proton. A three proton singlet at δ3.79 was assigned to the ester methyl group. The aromatic protons appeared as multiplets at δ6.79-7.22. The NH proton appeared as a singlet at δ8.88.

The ^{13}C-NMR spectrum ($CDCl_3$, 75 MHz) of (19R)-epimisiline showed 21 carbon resonances. The multiplicity assignments were made on the basis of polarization transfer experiments (DEPT).

The ^{13}C-NMR shifts are presented around structure **45.** The 2D NMR experiments (COSY-45 and 2D J-resolved) were also carried out to determine the ^{1}H-^{1}H coupling interactions and multiplicities of the proton signals respectively. On the basis of the above spectral data, structure **45** was assigned to (19R)-epimisiline.

(19S)-Epimisiline (46)[91]

The UV spectrum (MeOH) of (19S)-epimisiline was characteristic of an anilino-acrylate chromophore showing absorptions at 226, 297 and 328 nm. The IR spectrum ($CHCl_3$) showed intense absorptions at 3500 cm^{-1} (O-H), 3350 cm^{-1} (N-H) and 1680 cm^{-1} (α,β-unsaturated C=O).

The HRMS afforded the molecular ion peak at m/z 368.1743, corresponding to the molecular formula $C_{21}H_{24}N_2O_4$, indicating ten double bond equivalents in the molecule. The mass fragmentation pattern was similar to that of (19R)-epimisiline[91].

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz) corresponded closely to that of (19R)-epimisiline[91], the major differences appearing at the chemical shifts for C-19H which appeared at δ3.59, 0.24 ppm downfield than the chemical shift of C-19H in (19R)-epimisiline. This suggested that (19S)-epimisiline was the C-19 epimer of (19R)-epimisiline.

The ^{13}C-NMR spectrum ($CDCl_3$, 75 MHz) of (19S)-epimisiline was also very similar to that of (19R)-epimisiline[91]. Particularly revealing was the fact that the chemical shifts of C-21 in both compounds was virtually identical. This supported the conclusion that the epoxide function was in the β-configuration in (19S)-epimisiline[91], since in the α-configuration C-21 would have been expected to resonate downfield. These results indicate that the only point of structural difference between (19R)-epimisiline **(45)** and (19S)-epimisiline lay in the stereochemistry of the C-19 hydroxyl group. The ^{13}C-NMR chemical shifts are presented around structure **46.** The 2D NMR experiments (COSY-45 and 2D J-resolved) also served to establish structure **46** for (19S)-epimisiline.

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THE USE OF NATURAL IMMUNE ENHANCERS IN THE TREATMENT OF FAR-ADVANCED CANCER

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ABSTRACT

In view of the fact that the incidence and mortality of cancer are increasing, and the fact that all cancer patients have an underlying immune deficiency which is not helped but rather aggravated by the conventional cancer treatment modalities, i.e. surgery, radiation therapy, and chemotherapy, it becomes increasingly desirable to have some effective nontoxic immune enhancing modalities, which can be used by themselves or in combination with the conventional cancer therapies.

At the Akbar Clinic and the Institute of Islamic Medicine for Education and Research, we have been evaluating various natural substances with regard to their effect on the immune system of the human body. The preliminary results of our controlled studies in human volunteers indicate that the Black Seed, garlic, and bee honey, as well as the natural pure nutrients, have an immune enhancing effect. Certain vitamins, such as C, E, and Beta Carotene, and certain minerals, such as germanium and selenium, as well as the reduction of stress and the restoration of a positive mental and spiritual attitude, are also known to have an enhancing effect on the immune system.

We have combined all the above-listed modalities in what we call the Multimodality Immunotherapy Program (M.I.P.), and we are currently evaluating its effect in patients with far-advanced cancer who have failed to respond to, or even failed to qualify for, the conventional cancer treatment modalities. The M.I.P. is used in some patients as the only treatment given, while in others it is combined with conventional therapies. The program is in its second year, and it is therefore too early to give any cure rates or long-term results. However, the early results are exciting and very promising. In patients who completed the intensive course of the M.I.P., some tumors completely disappeared, and some were arrested and in a way started behaving like benign tumors. In all patients, there was a measurable enhancement of one or more of the immune functions as determined by monitoring of the T and B cell profiles with the T cell subsets, as well as the Natural Killer cell activity. This is a preliminary report of this alternative treament approach for patients with cancer.

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FUNCTIONAL AND BEHAVIOURAL TERATOLOGICAL STUDIES OF A CERTAIN HERBAL FORMULATION IN RATS

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Abstract:

The herbal formulation consists of the roots of *Withania somnifera* Linn., *Pyrethrum indicum,* D.C., corm of *Merendra persica* Linn. and rhizome of *Alpinia galanga* Wild, and is being used in treatment of Rheumatoid Arthritis in Islamic Centre for Medical Sciences. Female rats (Fo) were given the aqueous extract of the formula in two dose levels (400 and 800 mg/rat/day as 20 and 40 mg/ml of drinking water for low (L) and high (H) dose groups respectively), 15 days before placement for mating, through gestation and parturition until day 25 *post-partum.* The physical and behavioural development of their offspring (F_1) were assessed up to 90 days of age.

Treatment had no effect on body weight gain of Fo females during pregnancy or length of gestation. There was a dose related increase in the number of live pups and female ratio per litter. The number of stillbirths in the H group, however, was significantly higher. Body weight gain was less in the treated males and females upto 90 days of age. There was a delay in ear and eye opening of L group. Hair growth of L and H offspring was advanced than the control while there was no difference between the groups in survival, tooth eruption, descent of testicles or vaginal opening.

Assessment of reflex and motor development of F_1 animals revealed a loss of cliff avoidance of H group at day 7 of age, and an increase in grip strength of L group at day 13 of age, while there was no difference between the groups in surface or mid-air righting at 4-6 and 16-21 days of age respectively, in swimming performance at 5-14 days of age and in ability to stay on a rotating rod at 30-37 days of age.

There was no difference in an auditory startle response at 14 days of age or jumping down test at 10 days of age. At day 21 of age, however, more of H group jumped down from the high height than the controls.

Assessment of behaviour of F_1 offspring, 40-90 days of age, showed that treated males were hypoactive during the first trial in the activity cage. There was no difference in exploration or repetitive behaviour of treated females on a hole board, while H group had higher emotionality during the first trial. A significant dose related increase (females) and decrease (males) in the number of conditioned avoidences. Male rats in both treated groups made more errors until learned a swimming maze.

When F_1 male rats were sacrificed at 120 days of age, a dose related increase in serum cholesterol and decrease in serum GPT levels was observed. An increase in serum glucose (18%) and blood urea nitrogen (14%) was also observed in H groups.

Fertility index of F_1 rats was 81.3, 59.1 and 95.0% for control, L and H groups respectively. The number of

F_2 pups born alive to the treated groups was significantly higher, and 72-93% of all pups survived up to day 21 of age.

Based on the functional alterations observed in the present study, it is advisable not to give these herbal agents to women during pregnancy or lactation period.

INTRODUCTION

From time immemorial, man has used the extraordinary medicinal properties of certain herbs either singly or in combination to treat several baffling diseases. The medicinal plants, *Withania somnifera, Pyrethrum indicum, Merendra persica* and *Alpinia galanga* have been advocated in the treatment of several diseases[1-5], such as rheumatism, sexual debility, liver and spleenic disorders. *Withania somnifera,* has been recommended as an uterine tonic in leucorrhoea and in the treatment of spermatorrhoea, premature ejaculation, constipation, chronic jaundice and fever[6-8]. The combination of these plants has been reported to be effective in the treatment of clinical arthropathies[9] and is being pharmaceutically formulated as tablets (RA) and used clinically in the Islamic Centre for Medical Sciences, Kuwait, for the treatment of rheumatoid arthritis. Earlier studies in our laboratory have indicated the anti-inflammatory[10] and anti-ulcer[11] activity of the formulation experimentally. Further, it was also reported that the RA extract did not exhibit teratogenic and mutagenic potentials in mice[12].

The requirement to test animals for postnatal effects of human medicines was introduced recently in several countries. In the U.K. the requirement was introduced in 1975 with general guidelines which state that, in the fertility and perinatal studies, in addition to testing the reproductive capacity of the offspring, the late effects of the drug on the progeny, in terms of auditory, visual and behavioural function should be assessed. Since, the RA preparation is the most commonly prescribed formula in our Centre, and an increasing number of patients are using it, including women during child bearing age, it was felt necessary to investigate its effect on postnatal physical, functional and behavioural development in the rat, in the course of assessment of their safety.

MATERIALS AND METHODS

The herbal formulation (RA) consists of the roots of *Withania somnifera* Linn. (Solanaceae), *Pyrethrum indicum,* D.C. (Asteraceae), corm of *Merendra persica,* Linn. (Liliaceae), and rhizome of *Alpinia galanga,* Wild. (Zingeberaceae) in ratio of 2:1:1:1 parts respectively.

Female albino rats (parental, Fo) weighing 230-260 g, were given the aqueous herbal extract, prepared as described previously[12], in two dose levels (400 and 800 mg/rat/day) as 20 and 40 mg/ml of drinking water for low (L) and high (H) dose groups respectively. The control group was given tap water. The extract was given to animals daily for two hours, a time which was sufficient for the animals to drink what was given to them. Treatment started 15 days before placement for mating and continuously, through gestation and parturition until day 25 post-partum. Mating was performed by placement of 3 females with one untreated male for 2 h (8-10 a.m.) for 5 consecutive days, and successful mating was confirmed by the presence of spermatozoa in the vaginal smear. Pregnant animals were caged individually, and within 24 h after parturition, the offsrping (F_1) were culled to 8 per litter and their physical and behavioural development were assessed up to 90 days of age. The reproductive performance of F_1 mature rats was also tested. The physical development of their offspring (F_2) was observed up to 21 days of age.

Physical development:

This was assessed by measuring or observation of the following parameters: survival and body weight at

different ages, ear opening at 2-3 days of age, hair growth at 3-5 days of age, tooth eruption at 9-12 days of age, eye opening at 14-16 days of age, descent of testicles at 27 days of age and vaginal opening at 30-42 days of age.

Reflex and motor development:

Surface righting reflex was assessed at 4-6 days of age, cliff avoidence at 7-9 days of age, swimming performance at 5-14 days of age, grip strength at day 13 of age, righting in mid-air at 16-21 days of age, and ability to stay on a rotating rod[13] at 30-33 days of age.

Sensory development:

Development of functional hearing was assessed by measuring an auditory startle response at day 14 of age. Olfaction and visual development were assessed in a jumping down test at 10 and 21 days of age respectively[14].

Behaviour:

Spontaneous activity, emotionality and habituation of F_1 offspring were measured using an activity cage (Ugo Basile, Italy) at 39-50 days of age, exploration and repetitive activity were assessed using the hole-board apparatus[15] at 70-75 days of age, learning ability was assessed using swimming E-shape maze and automatic reflex conditioner (Ugo Basile, Italy) at 70-90 days of age. Most of these tests have been reported in details[16-18].

Fertility and reproductive function of F_1 rats:

At 90-120 days of age, males and females in each group were mated by placing one male with one female (sibling matings are avoided) for 5 successive days, and then separated and returned to single cages. Females that had not littered after the maximum time allowed for littering subsequent to mating are judged not to be pregnant and were remated for another 5 days. Pregnant females were allowed to deliver and nurse their young. The physical development of the offspring (F_2) was observed up to day 21 of age as shown for F_1 rats.

Biochemical functions:

At 120 days of age, F_1 males were sacrificed after an overnight food deprivations. Blood was collected from the retro-orbital sinus under Nembutal anaesthesis (40 mg/kg, i.p). The blood was allowed to clot, and serum was separated by centrifugation and used for the determination of glucose, blood urea nitrogen (BUN), albumin, total proteins, total bilirubin, cholesterol, triglycerides, creatinine, alkaline phosphatase, glutamic oxalacetic transaminase (GOT), and glutamic pyruvic transaminase (GPT), using Automatic Clinical Analyser (ACA, SX, Dupont).

Statistical methods:

The results obtained for males and females seperately and in combination for each group were analyzed using Student's 't' test or Chi-square test where appropriate.,

RESULTS

The effects of RA on fertility, gestation and litter size are shown in Table 1. Out of 20 females in each group, at the start of the experiment, only 7,7 and 6 animals were pregnant at term in the control, L and H groups respectively. Treatment had no effect on length of gestation period, or body weight gain of parental

animals during pregnancy. Control rats increased in weight from 273 ± 8.5 g to 365 ± 13.2 g, L group from 242 ± 4.5 g to 332 ± 7.6 g, and H group from 236 ± 14.2 g to 341 ± 13.7 g, at day 1 and 21 of gestation respectively. Two animals from the H group had 12 and 4 stillbirths ($P<0.001$). There was a dose related (though non-significant) increase in the number of implantation sites, live pups (F_1), and female ratio per litter. External examinations of the pups, soon after parturition, did not show any abnormalities.

Physical development of F_1 offspring:

Survival and body weight is shown in Table 2. All F_1 offsprings in the three groups survived until the end of the experiment, except of one male from the H group which died at 29 days of age. There was no significant difference between the groups in body weight at 2 days of age. Body weight gain, however, was less in the treated males and females up to 90 days of age. The body weight of treated animals was significantly less than that of the controls at 90 days of age, and was dose related in males but not so in females.

Other physical developmental parameters are shown in Table 3. There was a delay in ear and eye opening of L group at 2 and 14 days of age respectively. Hair growth of L and H offspring was advanced than that of the controls at 3 and 4 days of age respectively. There was no difference between the groups in time for tooth eruption, descent of testicles or vaginal opening.

Reflex and motor development:

Assessment of reflex and motor development of F_1 animals (Table 4) revealed a dose related loss of cliff avoidence at day 7 of age, the number of H (male+female) animals which backed away from the cliff, was significantly less than the controls. By 9 days of age, however, all animals in the three groups succeeded to perform the test. At day 13 of age, both males and females of L group, remained longer time hanging on horizontally stretched wire (forepaw grip strength). On the other hand, there was no difference between the groups in the number of animals that succeeded to turnover to right position within 15 seconds when placed on back on flat surface (surface righting) at 4-6 days of age, or when dropped, dorsal side downwards from height of 30 cm (mid-air righting) at 16-20 days of age, in straight line swimming and angle of body to surface during swimming at 5,8,11 and 14 days of age, and in ability to stay on a rotating rod at 30-33 days of age.

Sensory development:

The results are shown in Table 5. In the jumping test, pups were placed on a platform and allowed to jump from a low or high height to either the home cage or an empty cage at 10 and 21 days of age. At 10 days of age, when the eyes of the pups were still close, about 60-70% of the pups in all groups jumped down from the low height to the home cage. The remaining pups, mostly did not leave the platform, with small number jumped down to the empty cage. At day 21 of age, when eyes are opened, 70-80% of pups jumped down to the home cage from the low height. More of the H group pups jumped down from the high height than the controls at day 21 of age.

There was no significant difference between the groups in an auditory startle response at day 14 of age.

Behaviour of offspring:

Activity cage: Animals were tested in pairs (males or females) in an activity cage for one daily 5 min trial on 3 successive days at 39-50 days of age. The activity (in an arbitrary scale) and number of fecal boluses deposited were recorded. The results show that males in both treated groups were hypoactive during the first trial (Table 6), while there was no difference between the groups in activity during the second and third trials (as a measure of habituation) or in the number of fecal boluses deposited (as a measure of emotionality).

Head dipping test: At 70-75 days of age, the female offspring were allowed a 2 min trail on the hole-board apparatus on 3 successive days. Male offspring were not tested because of their large size at that age. The number of head dips into different holes (first dips, as a measure of exploration), or into same hole with no intervening locomotion (repeated dips, as a measure of repetitive behaviour), as well as fecal boluses deposited were recorded. There was no difference, in exploration, repetitive behaviour, or habituation between the groups. Females of H group, however, showed higher emotionality during the first trial, and those of L group showed less emotionality during the third trial (Table 6).

Conditioned avoidence learning: At 70-80 days of age each animal, after a familiarisation period of 5 min, was given 20 conditioned stimuli (light/buzzer); unconditioned stimuli (electric shock to feet) pairings daily at 20 second intervals for 5 successive days. The number of successful avoidences and total waiting time (seconds) was recorded. Males showed a dose related decrease in the number of successful avoidences (Table 7) with significantly increased waiting time.

Swimming maze: At 80-90 days of age, the animals were placed at start in central short arm of E-shape water-filled maze with escape ladder at end of right hand arm on first day, left hand arm on second day. The time taken to escape and errors made were recorded. The trials were run at 30 min intervals until 3 successive trials with no errors were performed. Males of L group took more time and made more errors until learned the maze on the first day, while those of H group made more errors to learn the maze on the second day (an opposite response to that previously learned). There was a tendency of the L and H females of making less errors to learn the maze on both days, the difference, however, was not significant (Table 7).

Biochemical functions:

When F_1 males were sacrificed at 120 days of age, after an overnight food deprivation, a dose related increase in serum cholestrol and decrease in serum GPT levels was observed. An increase in serum glucose (18%) and blood urea nitrogen (14%) was also observed in H groups. There was no significant difference between the groups in serum albumin, total proteins, total bilirubin, triglycerides, creatinine, alkaline phosphatase, or GOT levels (Table 8).

Fertility and reproductive function of F_1 rats:

Results are shown in Table 9. There was no significant difference between the groups in Fertility index of F_1 rats. The number of F_2 pups born alive to the treated groups was larger and significantly so for H group. There was a significant reduction in survival of L offspring compared to that of the controls. F_2 male offspring had matched body weight in the three groups, while females of treated groups were born heavier. Body weight gain of H male and L and H female offspring was significantly lower than that of the controls.

Physical development of F_2 offspring:

Results are shown in Table 10. Offspring of L rats had delayed ear opening at 3 and 4 days of age. Hair growth, tooth eruption and eye opening was advanced in both L and H groups than the control group. There was no difference between the groups in surface righting reflex.

DISCUSSION

The low (L) and high (H) doses used in the present experiment (given in the drinking water) were 4 and 8 times, respectively, that shown earlier to produce an anti-inflammatory activity when given orally to rats [10], and that of the maximal clinical dose of RA (4 g/patient, daily), based on surface area ratio.

Administration of the extract was started 15 days before mating, through gestation and parturition, until day 25 post-partum. Therefore, treatment covered about 3 estrus cycles before mating to assess the effect on fertility of females (males were untreated). It was found that treatment with the extract had no effect on fertility of parental females. A low fertility rate (30-35%), however, was observed in all groups. In the present experiment mating was allowed only for two hours each morning for 5 successive days. This procedure was followed, instead of caging females with males overnight or continuously for 5 days, to determine the time of mating with minimal variability, and to avoid non-specific changes in gestational period and body weight of pups.

Treatment had no effect on body weight gain of parental animals (Fo) during pregnancy or on length of gestation. Two animals from the H group had all their pups delivered dead, which could be due to difficulty in parturition. Examination of these stillbirths showed no obvious reason for their death.

A dose related (though non-significant) increase in the number of implantation sites, live pups (F_1), and female ratio per litter was observed. A similar effect was shown earlier in mice[12]. The effect on the number of implantations and litter size could be due to maturation of more ovarian follicles with subsequent ovulation, and/or enhancement of implantation of the zygotes after fertilization. The RA extract was shown[12] to possess a slight but significant estrogen-like activity in both non-overiectomized and overiectomized mature mice. The latter effect could be induced by the steroidal lactones (Withanolides), present in *Withania somnifera*[19], a major component of RA extract. The change in sex-proportion could be due to variation in vaginal and intracervical pH as a result of direct actions of the extract or through a hormone-mediated effect. Changes in pH levels affect the motility of spermatozoa containing X and Y chromosomes[20]. In man, male zygotes are formed earlier in the cycle than female zygotes[20,21], and this is related to maternal hormone levels[22]. RA extract induced estrus cycle in mice[12], and this could mean that, at the time of mating, the treated animals were already late in the cycle which favours fertilization of female zygotes.

External examination of the pups soon after parturition did not show any malformation. This was supported by the finding that all offspring born alive, survived until the end of the experiment, except one male pup from the H group. Neonatal mortality may be due to the offspring being anomalous in some subtle way[23], and these anomalous offspring are usually destroyed by the mother[24]. Studies in mice, showed no association of RA treatment with malformations[12].

No effect on maternal body weight gain during gestation period, as well as, on offspring birth weight was observed. That eliminates the possibility of undernutrition during gestation period as a result of giving the extract in the drinking water. Body weight gain of treated F_1 offspring during preweaning and upto 90 days of age, however, was less than that of the controls. This could be due to undernutrition during lactation period. It has been reported[25,26] that, undernutrition during gestation results in low birth weight, but by weaning "catch up" is observed and there is no difference in body weight of adults compared with controls. Undernutrition during lactation, however, results in low weaning body weight and no subsequent "catch up". In neither case is there any increase in pup mortality[25,26]. Therefore, the effect of treatment in the present experiment, is similar to undernutrition during lactation period; possibly due to decreased lactation or change in maternal behaviour towards their offspring. The decrease in body weight gain might have influenced the observed delay in ear and eye opening of L pups at 2 and 14 days of age respectively. A similar effect, however, was not seen in the H group. No effect on other physical developmental parameters was observed.

Reflex and motor development:

These tests are designed to assess the rate of development of basic motor skills and fine motor co-ordination[14]. No differences between the groups were observed in reflex and motor development. Treatment had no effect on surface or mid-air righting, in swimming performance, or in ability to stay on a

rotating rod. These tests were carried out from early days of life (day 4) upto 37 days of age. A loss of cliff avoidence of H animals was observed at day 7 of age. Cliff avoidence is a measure of maturity of forelimb development (pushing the body sideways or backwards when placed on the edge of a cliff or tabletop looking down), the stimulus being presumably tactile to the paws, nose and vibrassae[14]. Other tests for motor development did not show delayed forelimb maturation. Therefore, poor motivation of the test could result in the observed differences. The increase in grip strength of treated offspring is not dose related and can be influenced by the relatively lower body weight of these animals. It has been shown previously that, undernutrition of rat offspring during suckling period produced cerebellar growth retardation accompanied by motor deficits[25,26]. In the present experiment, however, rat offspring had reduced body weight gain but without any signs of motor deficits or cerebellar retardation. That could be due to less severe undernutrition in the present experiment compared to that reported earlier[25,27].

Sensory development:

There was no difference between the groups in an auditory startle response which measures development of functional hearing. Olfaction and visual ability were measured in a jumping-down test. The test was performed at day 10 of age, when the eyes of the pups were still closed, to measure olfaction (heat sensation could also be involved). The results showed no difference between the groups at that age. At day 21 of age, when the eyes were opened, the test can measure visual ability[14]. In the present experiment, more of H group pups jumped down from the high height than the controls at 21 days of age. This may indicate a visual deficit (depth perception deficit), abnormally high motivation to join litter mates, or lack of fear of jumping from heights.

Behaviour:

Activity, emotionality and habituation[28] were assessed using the activity cage. Animals were used in pairs and tested for 5 min daily trial on 3 successive days. Treated males were hypoactive during the first trial. Exploration, repetitive behaviour, emotionality and habituation, were also assessed on a hole board apparatus[15]. Females were tested singly for 2 min daily trial on 3 successive days. It was difficult to test males on the hole board because they were large in size at the time of testing (70 days of age). H animals showed higher emotionality during the first trial and L animals showed lower emotionality during the third trial. Differences in emotionality became clear when the animals tested individually using the hole board, than when tested in pairs using the activity cage. Unfamiliar situation induces fear, due to anxity exhibited in animals when placed in a new environment.

Learning ability of the offspring were tested using conditioned avoidence and swimming maze. In both tests, treated males were slower, while treated females were faster to learn both tasks. These results may be difficult to interpret, but the observed sex difference in learning ability may emphasise the influence of extract administration during vulnerable periods of development on the hormonal status of rat offspring. The extract was found to have a weak estrogenic and androgenic activity in female and male mice respectively[12].

Biochemical functions:

When male offspring (F_1) were sacrificed at 120 days of age, a slight but significant increase in blood glucose and urea nitrogen, as well as, a decrease in GPT levels were observed in the H group. These changes may indicate an elevation of blood glucose through promotion of gluconeogenesis from amino acids, and decreased carbohydrate utilization[29]. The increase of blood urea nitrogen without a concomitant increase of creatinine may indicate a case of mild prerenal azotemia in these rats[30].

Reproductive performance of offspring (F_1):

There was no significant difference between the groups in fertility. The number of live pups (F_2) born to the treated offspring (F_1) was significantly higher, an effect which is similar to that observed in the parental (Fo) animals. The survival of F_2 offspring in the L group was slightly lower at day 21 of age. Again, similar to F_1 rats, L and H, F_2 offspring were born with virtually similar body weight. Their body weight gain, however, was lower than that of the controls up to day 21 of age, which may indicate some undernutrition during lactation period.

The results of the present study may indicate that administration of RA herbal extract before and during pregnancy and lactation periods, did not produce any structural malformations in rat offspring. It has no effect, on fertility of parental rats or of their offspring, reflex and motor development and sensory development of F_1 offspring. The significant findings observed, were an increase in the number of live pups born to the parental and F_1 rats, an increase in the female ratio of F_1 rats, a decrease in body weight gain of both F_1 and F_2 rats, as well as, changes in emotionality, learning ability and biochemical functions. These results may support an earlier view[31], that postnatal functions does, at least in some cases, appear to be more sensitive indicator of teratogenic effects than physical malformations.

According to the suggestion of Rodier[17] that, an agent which effects a functional alteration must be regarded as hazardous, even if it cannot be shown to produce morphological changes, and based on the findings of the present study, it is advisable, therefore, not to give these herbal agents to women during pregnancy or lactation period.

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TABLE 1: EFFECT OF THE HERBAL EXTRACT (RA) GIVEN 15 DAYS BEFORE MATING AND THROUGH GESTATION TO PARENTAL (FO) FEMALE RATS, ON FERTILITY, GESTATION AND LITTER SIZE.

	Control	RA(L) 400 mg/rat	RA (H) 800 mg/rat
No. of animals treated	20	20	20
No. of positive smears	13	14	10
No. of animals pregnant at term	7	7	6
Gestation period (days±s.e.m)	23.4 ± 0.29	23.4 ± 0.3	23.3 ± 0.33
Total no. of implantations / no. of dams[a]	60/9	60/8	60/6
No. of live pups/no. of dams (%)	41/7 (68)	47/7 (78)	35/4 (58)
Mean no. of live pups ± s.e.m.	5.86 ± 0.96	6.71 ± 0.7	8.75 ± 1.1
No. of males (%)	23 (56)	25 (53)	13 (37)
No. of females (%)	18 (44)	22 (47)	22 (63)

a: Implantation sites were counted, when all animals were killed at the end of the treatment period (25 days post-partum), 2 and 1 animals of control and L groups respectively had implantation sites and no live pups, 2 animals of H group had 12 and 4 stillbirths ($P<0.001$) and no live pups.

TABLE 2: EFFECT OF THE HERBAL EXTRACT (RA) GIVEN 15 DAYS BEFORE MATING AND THROUGH GESTATION AND PARTURITION UNTIL DAY 25 POST-PARTUM TO PARENTAL (FO) FEMALE RATS ON SURVIVAL AND BODY WEIGHT OF THEIR OFFSPRING (F_1) UPTO 90 DAYS OF AGE.

Day of Age	Males			Females		
	Control (22)	RA (L) (23)	RA (H) (10)	Control (16)	RA (L) (22)	RA (H) (20)
2	8.28±0.13	8.37±0.19	8.15±0.41	7.75±0.10	7.4 ±0.13	8.04±0.23
7	18.65±0.47	18.42±0.65	16.69±0.77*	17.36±0.47	15.65±0.18**	17.29±0.49
15	37.9 ±0.98	35.4 ±0.81	31.4 ±1.28**	33.2 ±1.03	31.0 ±0.68	32. 3±1.43
21	49.8 ±1.1	50.1 ±1.2	42.9 ±2.2 **	48.8 ±1.14	44.5 ±1.5	45.0 ±2.21
30	95.1 ±1.9	93.0 ±1.5	81.6 ±2.4 **	85.8 ±2.1	84.2 ±1.71	81.2 ±2.3
60	260.6 ±4.4	264.2 ±3.5	252.8 ±8.0	193.2 ±4.4	175.1 ±3.8 **	180.5 ±1.8 **
90	286.0 ±4.64	264.4 ±4.95**	259.7 ±8.7 **	202.9 ±4.78	176.6 ±5.85**	178.7 ±3.86**

Number of offspring at day 2 of age, after culling, is shown in parentheses, and one male from H group died at day 29 of age. Results are expressed as mean body weight g +s.e.m. and compared using Student's t test.
* $P < 0.05$ ** $P < 0.01$

TABLE 3: EFFECT OF THE HERBAL EXTRACT (RA) GIVEN 15 DAYS BEFORE MATING AND THROUGH GESTATION AND PARTURITION UNTIL DAY 25 POST-PARTUM TO PARENTAL (FO) FEMALE RATS ON PHYSICAL DEVELOPMENT OF THEIR OFFSPRING (F_1).

Number of offspring	Day of age	Control 38	RA (L) 45	RA (H) 30
Ear opening	2	35 (92.1)	30** (66.7)	28 (93.3)
	3	38 (100)	45 (100)	30 (100)
Hair growth	3	0 (0.0)	7** (15.6)	0 (0.0)
	4	2 (5.3)	7 (15.6)	8** (26.7)
	5	38 (100)	45 (100)	30 (100)
Tooth eruption	9	2 (5.3)	1 (2.2)	3 (10.0)
Lower incisors	10	18 (47.4)	19 (42.2)	11 (36.7)
	11	35 (92.1)	33 (73.3)	24 (80.0)
	12	38 (100)	45 (100)	29 (96.7)
Eye opening	14	17 (44.7)	10* (22.2)	18 (60.0)
	15	38 (100)	26 (57.7)	23 (76.7)
	16	38 (100)	44 (97.8)	30 (100)
Descent of testicles	27	22 (100)	23 (100)	10 (100)
Vaginal opening	30	0 (0.0)	3 (13.6)	0 (0.0)
	36	8 (50.0)	15 (68.2)	13 (65.0)
	42	15 (93.8)	22 (100)	20 (100)

Results are expressed as the number of offspring with positive findings (%) and compared using Chi-square test — *: $P < 0.03$ **: $P < 0.01$

TABLE 4: EFFECT OF THE HERBAL EXTRACT (RA) GIVEN 15 DAYS BEFORE MATING AND THROUGH GESTATION AND PARTURITION UNTIL DAY 25 POST-PARTUM TO PARENTAL (FO) FEMALE RATS ON REFLEX AND MOTOR DEVELOPMENT OF THEIR OFFSPRING (F_1).

Number of offspring	Age (days)	Control 38		RA (L) 400 mg/rat 45		RA (H) 800 mg/rat 30	
- Surface righting:	4	34	(89.5)	38	(84.4)	28	(93.3)
	5	38	(100)	42	(93.3)	30	(100)
- Cliff avoidance:	7	36	(94.7)	38	(84.4)	22	(73.3)*
	8	35	(92.1)	39	(86.7)	24	(80.0)
- Swimming performance:							
(A) Swimming at 30°angle	5	27	(71)	35	(78)	21	(70)
of body to surface	14	38	(100)	43	(96)	29	(97)
(B) Straight line swimming	5	8	(21)	17	(38)	2	(6.7)
	14	24	(63)	45	(100)	21	(70)
- Grip strength,[a]	♂ 13	12.2±1.67 (22)		19.8±2.35 (23)*		14.6±2.22 (10)*	
	♀ 13	10.3±1.21 (16)		16.6±2.05 (22)*		14.6±1.89 (20)*	
- Mid-air righting	16	23	(60.5)	27	(60)	16	(53.3)
	18	35	(92.1)	37	(82.2)	26	(86.7)
	20	37	(97.4)	44	(97.8)	28	(93.3)
Rotarod:							
1st trial (8 r.p.m.)	30-33	12	(31.6)	19	(42.2)	12	(41.4)
2nd trial (12 r.p.m.)		21	(53.3)	29	(64.4)	14	(48.3)
3rd trial (16 r.p.m.)		27	(71.1)	37	(82.2)	18	(62.1)

Results are expressed as number of animals succeeded to perform the test (%), and compared using Chi-square test.

a. Results are expressed as mean time (sec) taken until fall off the rod ± s.e.m. (Number of animals shown in parentheses). * $P < 0.02$

TABLE 5: EFFECT OF THE HERBAL EXTRACT (RA) GIVEN 15 DAYS BEFORE MATING AND THROUGH GESTATION AND PARTURITION UNTIL DAY 25 POST-PARTUM TO PARENTAL (FO) FEMALE RATS ON SENSORY DEVELOPMENT OF THEIR OFFSPRING (F_1).

Number of offspring	Day of age	Control 38	RA (L) 45	RA (H) 30
Jumping test:				
a. No. of pups jumping down to the home cage from low height (10 cm).	10	24 (63.2)	33 (73.3)	22 (73.3)
	21	26 (68.4)	38 (84.4)	25 (83.3)
b. No. of pups jumping down to the empty cage from low height (10 cm).	10	2 (5.2)	4 (8.4)	2 (6.7)
	21	3 (7.9)	2 (4.5)	3 (10.0)
c. No. of pups jumping down to either cages from high height (40 cm.)	10	6 (13.2)	14 (26.7)	4 (13.3)
	21	11 (10.5)	17 (28.9)	17* (40.0)
Auditory startle	14	38 (100)	40 (88.9)	30 (100)
	15	38 (100)	43 (95.6)	30 (100)

Results are expressed as the number of offspring with positive response (%) and compared using Chi-square test. *: $P < 0.02$

TABLE 6: EFFECT OF THE HERBAL EXTRACT (RA), GIVEN 15 DAYS BEFORE MATING AND THROUGH GESTATION AND PARTURITION UNTIL DAY 25 POST-PARTUM TO PARENTAL (FO) FEMALE RATS, ON BEHAVIOUR OF THEIR OFFSPRING (F_1) USING ACTIVITY CAGE AND HOLE BOARD AT 35 AND 70 DAYS OF AGE RESPECTIVELY.

	First trial	Second trial	Third trial
Activity cage:			
Control males (n=10 pairs)	377 ± 39.5	335 ± 48.4	330 ± 27.3
RA (L) males (n= 9 pairs)	266 ± 28.3*	210 ± 36.6	210 ± 21.9
RA (H) males (n= 3 pairs)	261 ± 17.9	229 ± 99.0	289 ± 75.9
Control females (6 pairs)	284 ± 34.3	278 ± 69.2	245 ± 56.8
RA (L) females (10 pairs)	268 ± 18.7	195 ± 20.7	242 ± 35.9
RA (H) females (9 pairs)	325 ± 28.6	343 ± 53.4	268 ± 34.3
Hole board:			
a. Mean No. of first dips			
Control females (n=16)	9.9 ± 0.88	8.5 ± 1.11	7.3 ± 0.93
RA(L) females (n=22)	11.2 ± 0.99	8.6 ± 0.93	6.5 ± 0.91
RA(H) females (n=20)	9.8 ± 0.83	10.3 ± 1.45	7.1 ± 0.93
b. Total No. of repeated dips/ No. of animals:			
Control females (n=16)	8/4	8/8	1/1
RA(L) females (n=22)	6/5	10/7	3/3
RA(H) females (n=20)	12/5	12/7	4/4
c. Total no. of fecal deposites/ No. of animals:			
Control females (n=16)	3/1	3/1	19/6
RA(L) females (n=22)	12/6	1/1	6/1**
RA(H) females (n=20)	17/7*	6/2	20/6

Activities of animals in the activity cage are measured on an arbitrary scale and expressed as mean ± s.e.m for each pair of animals and compared using Student's 't' test.

Results in b and c are compared using Chi-square test: * $P < 0.05$ ** $P < 0.01$

TABLE 7: EFFECT OF THE HERBAL EXTRACT (RA) GIVEN 15 DAYS BEFORE MATING AND THROUGH GESTATION AND PARTURITION UNTIL DAY 25 POST-PARTUM TO PARENTAL (FO) FEMALE RATS ON LEARNING ABILITY OF THEIR OFFSPRING (F_1) AT 70-90 DAYS OF AGE.

	Control	RA (L) 400 mg/rat	RA (H) 800 mg/rat
Conditioned learning:			
Total no. of avoidences (males) n=	7	7	6
1st day (%)	5 (3.6)	2 (1.4)	0 (0.0)
3rd day (%)	14 (10.0)	11 (7.9)	2 (1.7)
5th day (%)	33 (23.6)	24 (17.1)	8 (6.7)*
Total no. of avoidences (females) n=	6	7	4
1st day (%)	2 (1.7)	4 (2.9)	4 (5.0)
3rd day (%)	7 (5.8)	10 (7.1)	9 (11.3)
5th day (%)	4 (3.3)	47 (33.6)*	18 (22.5)*
Swimming maze:			
a. Males n=	14	14	9
Mean time (sec) taken to learn (right)	144.6±9.99	242.3±28.1**	109±14.8
Mean no. of errors to learn (right)	5.57±0.05	7.43±0.58*	6.1±0.95
Mean time (sec) taken to learn (left)	137.7±23.8	121.7±16.1	154±23.1
Mean no. of errors to learn (left)	5.93±0.74	6.0±0.71	8.44±0.44*
b. Females n=	7	8	8
Mean time (sec) taken to learn (right)	140.0±15.7	110±22.6	174±32.1
Mean no. of errors to learn (right)	7.57±1.02	5.88±1.06	6.38±1.07
Mean time (sec) taken to learn (left)	246±117.6	134.4±32.6	64.3±23.3
Mean no. of errors to learn (left)	6.71±0.89	5.0±1.07	4.5±1.05

Results are compared using Chi-square test (conditioned learning), and Student's t test (swimming maze). n = number of animals * $P < 0.02$ ** $P < 0.001$

TABLE 8: EFFECT OF THE HERBAL EXTRACT (RA) GIVEN 15 DAYS BEFORE MATING AND THROUGH GESTATION AND PARTURITION UNTIL DAY 25 POST-PARTUM TO PARENTAL (FO) FEMALE RATS ON BIOCHEMICAL FUNCTIONS OF THEIR MALE OFFSPRING (F_1) AT 120 DAYS OF AGE.

Number of animals	Control 14	RA (L) 400 mg/rat 13	RA (H) 800 mg/rat 9
Glucose (mmol/L)	4.43 ± 0.22	4.55 ± 0.18	5.22 ± 0.27*
Blood urea nitrogen (BUN) mmol/L	4.9 ± 0.17	5.20 ± 0.27	5.60 ± 0.23*
Albumin G/L	9.9 ± 0.29	8.8 ± 0.26	9.1 ± 0.30
Total proteins G/L	62.6 ± 0.75	60.7 ± 0.6	60.0 ± 1.70
Total bilirubin mmol/L	2.1 ± 0.13	2.3 ± 0.75	2.0 ± 0.20
Cholesterol mmol/L	1.11 ± 0.05	1.27 ± 0.05*	1.3 ± 0.04**
Triglycerides mmol/L	0.54 ± 0.04	0.47 ± 0.03	0.58 ± 0.23
Creatinine mmol/L	31.0 ± 1.3	29.0 ± 2.2	31.0 ± 3.0
Alkaline phosphatase U/L	100.0 ± 7.75	110.0 ± 5.4	99.0 ± 3.6
GOT U/L	104 ± 3.1	105 ± 2.4	106 ± 4.7
GPT U/L	50.3 ± 2.1	40.7 ± 1.3 **	39.1 ± 3.8 **

Results are expressed as mean ± s.e.m and compared using Student's 't' test * $P < 0.03$ ** $P < 0.01$

TABLE 9: EFFECT OF THE HERBAL EXTRACT (RA) GIVEN 15 DAYS BEFORE MATING AND THROUGH GESTATION AND PARTURITION UNTIL DAY 25 POST-PARTUM TO PARENTAL (FO) FEMALE RATS ON FERTILITY AND LITTER SIZE OF THEIR OFFSPRING (F_1), AS WELL AS ON SURVIVAL AND BODY WEIGHT OF THE SECOND GENERATION (F_2) DURING THE PREWEARING PERIOD.

	Control	RA (L) 400 mg/rat	RA (H) 800 mg/rat
No. of pregnant/No. mated (1st trial)	5/16 (31.3)	12/22 (54.5)	11/18 (61.1)
No. of pregnant/No. mated (2nd trial)	8/11 (72.7)	1/10 (10.0)	8/9 (88.9)
Total No. of pregnant/No. mated (%)[a]	13/16 (81.3)	13/22 (59.1)	19/20 (95.0)
Mean no. of live fetuses + s.e.m	5.62 ± 0.77	7.23 ± 0.82	7.53 ± 0.46 *
No. of stillbirths (%)	3 (3.95)	0	4 (2.30)
No. of males at day 1 of age (%)	42 (57.5)	51 (54.3)	73 (51.0)
No. of females at day 1 of age (%)	31 (42.5)	43 (45.7)	70 (49.0)
Total no. of offspring at day 21 of age (survival, %)	65 (89)	68 (72.3)	134 (93)
Body weight of males at day 2 of age	7.52 ± 0.24	7.46 ± 0.15	7.52 ± 0.18
Body weight of males at day 21 of age	38.1 ± 1.18	39.3 ± 2.12	32.6 ± 0.98**
Body weight of females at day 2 of age	6.95 ± 0.30	7.47 ± 0.18	7.60 ± 0.16*
Body weight of females at day 21 of age	36.4 ± 1.48	31.2 ± 1.31*	33.8 ± 1.13

a : Fertility index * : $P < 0.05$ ** : $P < 0.01$

TABLE 10: EFFECT OF THE HERBAL EXTRACT (RA) GIVEN 15 DAYS BEFORE MATING AND THROUGH GESTATION AND PARTURITION UNTIL DAY 25 POST-PARTUM TO PARENTAL (FO) FEMALE RATS ON PHYSICAL DEVELOPMENT OF THE SECOND GENERATION (F_2) DURING PREWEARING PERIOD.

	Day of Age	Control	RA(L) 400 mg/rat	RA(H) 800 mg/rat
Ear opening	3	54/65 (83.1)	47/94 (50.0)**	118/141 (83.7)
	4	65/65 (100)	81/94 (86.2)**	140/141 (99.3)
Hair growth	3	16/65 (24.6)	17/94 (18.1)	72/141 (51.1)**
	4	40/65 (61.5)	69/94 (73.4)	122/141 (86.5)**
	5	58/65 (89.2)	85/86 (98.8)**	136/140 (97.1)*
Tooth eruption	9	6/65 (9.2)	11/69 (15.9)	9/134 (6.7)
	10	21/65 (32.3)	35/69 (50.7)*	51/134 (38.1)
	11	30/65 (46.2)	50/69 (72.5)**	88/134 (65.7)**
	12	52/65 (80.0)	61/69 (88.4)	108/134 (80.6)
Eye opening	14	9/65 (13.8)	11/69 (15.9)	32/134 (23.9)
	15	21/65 (32.3)	46/69 (66.7)**	100/134 (74.6)**
	16	39/65 (60.0)	50/69 (72.5)	117/134 (87.3)**
	17	60/65 (92.3)	63/69 (91.3)	132/134 (98.5)
Surface righting	4	61/65 (93.8)	84/94 (89.4)	126/141 (89.4)
	5	62/65 (95.4)	85/86 (98.8)	139/140 (99.3)

Results are expressed as the number of offspring with positive findings/total number (%) and compared using Chi-square test. * $P < 0.05$, ** $P < 0.01$

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PHARMACOLOGICAL BASIS OF THERAPEUTIC ACTION OF A HERBAL FORMULA IN THE TREATMENT OF CHRONIC BRONCHITIS AND ASTHMA

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Abstract:

The crude aqueous extract of the herbal formula antagonised the spasmogenic effect of histamine on the isolated guinea pig ileum. It also exhibited, at higher doses, a blanket activity against acetylcholine, carbachol, 5-hydroxytryptamine, bradykinin, prostaglandins E_1, E_2 and $F_1 \propto$ and potassium chloride. It inhibited the contractile effect of $CaCl_2$ on depolarized ileum. On the rabbit jejunum, the extract induced dose-dependent relaxation; it also sensitized the tissue to the relaxile effects of epinephrine and isoprenaline, and inhibited the contractile effects of acetylcholine, carbachol and histamine. On the rat fundus, it effectively antagonised the contractile effects of 5-hydroxytryptamine and prostaglandins $F_1 \propto$ and $F_2 \propto$; on the rat uterus, it inhibited the contractions induced by PGE_1. On the guinea pig atria, the extract produced a stimulant effect but in substimulant doses, it reversibly inhibited the positive inotropic and chronotropic effects of histamine and isoprenaline.

The extract inhibited the Schultz-Dale reaction on the isolated ileal pieces of ovalbumin-sensitized guinea pigs; the degree of inhibition of antigen-induced contraction was dependent upon the dose of the extract. It also prevented the release of histamine (pharmacologically - active substances) from the lungs of sensitized guinea pigs challenged *in vitro* with specific antigen; it had similar effects on the release induced by compound 48/80. Further, it markedly reduced the degree of degranulation of messenteric mast cells induced by compound 48/80. To a separate group of guinea pigs, the extract was administered orally, daily, 4 days before and 3-4 weeks after sensitization. The ileum pieces from extract treated animals responsed adequately to the antigen as also to histamine. However, the release of histamine from the lung tissues of these animals, challenged *in vitro* with specific antigen was significantly lower than the non-treated animals.

The extract markedly increased the latent period of histamine aerosol-induced bronchospasm and the resultant convulsions in guinea pigs and protected 40% animals from dying. It inhibited the cutaneous hypersensitivity response in guinea pigs as also the increase in cutaneous capillary permeability induced by histamine, bradykinin or 5-hydroxytryptamine, and, to some extent, facilitated the resorption of fluid accumulation at the site of histamine or antigen injection.

The extract was devoid of anti-inflammatory effect. It had no effect on the travel rate of charcoal meal in the gastrointestinal tract of mice but significantly inhibited the carbachol-induced increase in the gastrointestinal motility. It did not affect the magnesium sulphate-induced fluid formation in the rat intestinal loop.

It did not produce any adverse side effect upto a daily dose of 40 gm/kg fed for 3 days in rats and upto 20 gm/kg fed for 4 weeks in guinea pigs.

INTRODUCTION

In the traditional system of medicine, numerous plants are reputed, for over the centuries, to exert beneficial effects in diverse types of acute and chronic affections of the respiratory tract[1,2]. Of these plants, one formula composed of nine ingredients, namely- dried fruits of *Vitis vinifera, Zizyphus vulgaris, Cordia latifolia, Malva sylvestris,* seeds of *Althaea officinalis,* rhizome of *Glycyrrhiza glabra,* whole plants of *Lavandula stoechas* and *Adiantum capillus veneris* and flowers of *Viola odorata,* has been recommended by the traditional medical practitioners for the treatment of chronic bronchitis and bronchial asthma[3,4,5,6]. Incidentally, many of these ingredients are also used, in one or the other combinations, in the treatment of chronic rhino-sinusitis, pharyngitis, laryngitis and pneumonia, and for other types of chronic catarrhal affections. Allama Kabeeruddin[7], the highly renowned philosopher-physician, classified these ingredients into 3 groups; this categorization was based on the works of his predecesors as well as on his own personal clinical experiences. Accordingly, he described that (i) *Viola odorata, Zizyphus vulgaris, Cordia latifolia, Malva sylvestris,* and *Althaea officinalis* act as a demulcent, relieve the irritation in the nose, throat and bronchi, suppress the bouts of cough and relieve the spasms of bronchial tube[7a]; (ii) *Lavandula stoechas, Adiantum capillus veneris* and *Glycyrrhiza glabra,* produce resolvent, deobstruent and expectorant effects, subside swelling of respiratory passage, dilate the bronchial tube and produce broncholytic effects[7b,c]; (iii) *Lavandula stoechas* and *Viola odorata* with *Vitis vinifera* act also as laxative and carminative and thus reduce the intra-abdominal pressure over the diaphragm and intrathoracic organs[7d] thereby relieving the chest distress by complimentary action. Notably, the decoction of this formulation is being used effectively to control the incidences of chronic bronchitis and asthmatic attacks in patients attending certain clinics of herbal treatment*. However, studies on possible mechanism of its action are apparently lacking. The present investigation was, therefore, undertaken to systematically evaluate the pharmacological basis of thereapeutic action of this formula in chronic bronchitis and bronchial asthma or the chronic airway obstruction.

MATERIALS AND METHODS

Extraction procedure:

The fruits of *Zizyphus vulgaris* and *Vitis vinifera* were deseeded, the remaining plant materials crudely pulverised, and extracted with distilled water at room temperature (22-24°C) for 24 hours; to each 100 gm of material 1 litre water was added. Thereafter, the supernatant was filtered through muslim cloth. The filtrate was evaporated, under the running exhaust, to desired concentration and kept frozen for subsequent use, when it was pre-warmed to room temperature.

Animals:

Inbred strains of rats, mice, guinea pigs and rabbits of either sex were used in the present study. The animals were maintained on standard pellet diets and *ad lib* water. Guinea pigs were also given additional multivitamins mixed with drinking water.

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* Government Nizamia General Hospital, Hyderabad (India) and in over 200 Government Dispensaries in Andhra Pradesh (India). Also, at the Islamic Centre for Medical Sciences, Ministry of Public Health, Kuwait.

Isolated tissues:

Pieces of *guinea pig ileum, rabbit jejunum, oestrogenized rat uterus*[8], *rat fundus*[9] *depolorized guinea pig ileum*[10], and *isolated guinea pig atria*[11], were suspended in thermostatically controlled 10 ml capacity isolated tissue bath containing Tyrode (37°C), Ringer (37°C), deJalon (31°C), Krebs (37°C), potassium Ringer (37°C) and Ringer-Lock (30°C) solutions respectively; the solutions were continuously bubbled with air. The contractions were recorded on a smoked drum with a simple lever (magnification 1:7). For oestrogenization[12], adult female non-pregnant rats received oestradiol benzoate (0.1 mg) in 1 ml arachis oil intraperitoneally, daily on 2 successive days; the animals were sacrificed 24 hr after the last injection. For guinea pig ileum and rabbit jejunum, the animals were denied food, but allowed *ad lib* water, for 24 hr before sacrifice.

A 3-5 minute time cycle was followed. Contact period for different spasmogens was 25-30 seconds on guinea pig ileum and rabbit jejunum, and 60-90 seconds on rat uterus and rat fundus. The extract was allowed to act on the tissue for 60 seconds before addition of spasmogens. The tissue was repeatedly washed with fresh physiological solutions after each addition of drugs until the original state of the tissue was obtained.

Anti-Anaphylactic studies (Schultz-Dale reaction):

(a) *Sensitization procedure:* Guinea pigs weighing between 500 and 600 gm were used. The animals were actively sensitized[13] using fresh egg-white (3-5 ml of 25% v/v solution in normal saline) intraperitoneally. Booster dose of the antigen was administered via the same route 3 days after the first administration.

(b) *Treatment schedule:* The sensitized guinea pigs were divided into control group and a test group. The former were kept on water while animals in the latter group were each given in place of water, 50 ml of diluted extract (corresponding to 20 gm of plant material extract) per day. The treatment schedule was followed throughout the sensitized period of 3-4 weeks. Another group of non-sensitized animals were fed with same quantity of the extract for similar periods.

(c) *Anaphylactic contractions:* The animals were sacrificed after the sensitization period. The entire ileum was dissected out, cut into 3 cm long pieces and cleaned. The pieces were mounted vertically in a 10 ml organ bath as per the procedure described above for the isolated guinea pig ileum.

Anaphylactic contractions were elicited by the addition of varying doses of antigen and recorded. The antigen (egg-white 25%) dose ranged between .01 to .04 ml/ml bath fluid. Individual piece was discarded after one exposure to the antigen. The extract was added 1 minute prior to the antigen.

Mediator release from the lung tissue:

Control and sensitized animals were sacrificed by cervical dislocation followed by ex-sanguination to prevent blood from being aspirated into the lung[14]. The dissected lung was washed free of blood by passing aerated Tyrode solution through the pulmonary artery.

Approximately 0.5 to 1 gm wet weights of the washed lung tissues, kept in warm aerated Tyrode solution (100 mg tissue per 2 ml Tyrode), were challenged with 0.2 ml of antigen. Simultaneously, equal number of pieces were exposed to 200 mg of the extract for about 30 minutes; thereafter, the tissue was transferred to normal Tyrode solution and challenged with 0.2 ml of antigen.

In another set of experiments, the lung pieces from nonsensitized guinea pigs were exposed to 0.1 ml of 0.1% compound 48/80; concomitantly, equal number of pieces were exposed first to 200 mg of the extract and then to compound 48/80 (0.1 ml of 0.1% solution).

The exposure time either to the antigen or to compound 48/80 ranged between 15 to 20 minutes after which 1 ml aliquots of the solution were withdrawn and assayed on the nonsensitized atropinized guinea pig ileum. A dose-response curve using varying concentrations of histamine dihydrochloride, up to 30 ng/ml, on the same piece of ileum was plotted to obtain a calibration curve. The quantity of mediator released from the lung was estimated as histamine equivalents from this curve. For the release of mepyramine resistant spasmogens, the aliquots were assayed in the presence of mepyramine maleate at a final bath concentration of 10 ug/litre. Contractions caused by mepyramine-resistant spasmogens released per gm of lung tissue were expressed as per cent the contractions caused by 30 ng/ml of histamine dihydrochloride in the same non-sensitized ileal piece.

Cutaneous hypersensitivity:

The guinea pigs were sensitized with egg albumin as per the method described above. Three weeks after sensitization, Evans Blue (5 mg/kg) was injected, intravenously, either through the marginal ear vein or penal vein, 30 minutes before the intradermal injections (in the prepared abdominal region) of the antigen. At some spots, varying concentrations of extract was injected 10 minutes prior to the injection of antigen at the same spots. The volume of fluid injected at any single site and at any single time was 0.1 ml. The increase in permeability (wheal formation) was assessed[15] at 15 min, ½, 1, 2, 3 and 4 hour post-injection. The intensity of the increase in permeability was graded as +, ++, +++ and ++++ indicating mild, moderate, intense and severe reactions[16].

Cutaneous capillary permeability:

The method described above was followed except that the guinea pigs were not sensitized and the antigen was not injected intradermally. This study was also done in rabbits[17]. Histamine, bradykinin and 5-hydroxytryptamine were used as standard capillary permeability-increasing agents. The effect of extract was compared with mepyramine maleate.

Messenteric mast cells:

The messenteric tissues from the normal (nonsensitized) guinea pigs were exposed *in vitro* to compound 48/80 for 30 minutes. In some experiments, the messenteric tissues were first exposed to the extract for 30 minutes and then to compound 48/80 for another 30 minutes period. Thereafter, the tissues were spreaded over glass slides and stained[18]. The degree of degranulation was observed microscopically (× 40).

Histamine-induced bronchospasm:

Guinea pigs of either sex (600-700 gm) were exposed[19] to finely atomized mist of histamine dihydrochloride (1.5 per cent w/v) into aerosol chamber (Ugo basile, Italy). Compressed air at a constant pressure of 200 mm Hg was used to operate the nebuliser. The extract (20 gm/kg) was fed orally, daily, for 3 days, before the animals were exposed to the histamine aerosol. In other group of animals, mepyramine maleate (5 or 15 mg/kg) was injected intraperitoneally 30 minutes before exposure[20]. The time of onset of anoxic convulsions was recorded. The animals not showing convulsions upto 6 minutes after the start of histamine aerosol were regarded as completely protected.

Carrageenan-induced inflammation:

Acute inflammation was induced in the right hind paw of rats (either sex; 200-300 gm) by single sub-plantar injection of 0.1 ml of 1% solution of carrageenan[21]. The paw volumes were determined by means

of a plethysmometer (Ugo basile, Italy). Animals were pretreated orally, daily, with different doses of the extract for varying periods, the last administration being 1 hr before carrageenan.

Cotton pellet granuloma:

Sterile cotton pellets 10 mg each were implanted[22] bilaterally in pectoral and groin regions of rats under ether anaesthesia. The pellets were dissected out on the 7th day and wet and constant dry weights recorded. Drugs were administered once daily, orally, starting one day prior to the implantation of pellets.

Travel of charcoal meal:

Adult mice (25-30 gm) of either sex were denied food for 24 hr but offered water *ad libitum.* Charcoal meal[23] was prepared by suspending 1 gm finely powdered activated charcoal in 10 ml of 25% gum acacia in water. The mice were given the extract, orally, 30 minute before the charcoal meal (0.2 ml). Twenty minutes after charcoal meal feeding, the mice were sacrificed[24]. The abdominal cavity was opened and the entire small intestine from pylorus to ileocaecal junction was then gently freed by cutting the intestinal edge of the messentry. The freed intestine was gently placed, without stretching, in a straight line on a white filter paper. Length of the entire small intestine as also the portion traversed by dark-coloured charcoal meal were measured. Percentage of the small intestine length travelled by charcoal was then calculated.

Fluid accumulation in intestinal loop:

Adult rats (200-300 gm) of either sex were denied food for 24 hours but allowed *ad lib* water. Abdomen was opened under pentobarbitone anaesthesia and, extending from 3 cm below the pylorus, a 30 cm long intestinal loop was prepared by two ligatures[25,26]. Magnesium sulphate (2 ml of 15% solution) was injected in the loop. In one group of animals, the extract was injected directly into the loop 10 minutes before magnesium sulphate; in another group of animals, the extract was fed one hour before ligation and magnesium sulphate injection. Loop fluid was collected after 1, 2 or 3 hr and measured.

RESULTS

Isolated tissues:

Guinea pig ileum:-

The extract did not exert any direct effect of its own on the isolated guinea pig ileum upto a dose of 100 mg/ml. It however, inhibited the contractions induced by histamine (23 experiments). The antagonism was proportional to the dose of the extract. Thus 10, 20, 40, 60 and 80 mg/ml of the extract inhibited the histamine response (10 ng/ml) by 12.32, 22.23, 57.94, 70.05 and 86.93 per cent respectively. The ED_{50} for histamine was calculated to be 35.8 mg/ml. Antagonism by the smaller doses of extract was quickly reversible but by the higher doses it persisted for longer time. Antagonism could be repeatedly elicited on the individual tissues and it could be overcome by increasing the dose of histamine.

At relatively higher doses, the extract also produced dose-dependent inhibition of the spasmogenic effects of acetylcholine (6 experiments), carbachol (7 experiments), 5-hydroxytryptamine (5 experiments), bradykinin (3 experiments), prostaglandins E_1 (4 experiments), E_2 (5 experiments), and $F_1 \propto$ (2 experiments) and potassium chloride (4 experiments). The ED_{50} for respective agonists were calculated to be 60.2, 65.4, 50.2, 75.3, 68.2, 70.2, 64.3 and 61.6 mg/ml respectively.

On the depolarized tissue (5 experiments), the extract (10-30 mg/ml) reversed the carbachol-induced contracture and inhibited, by about 30-60%, the calcium chloride (1 mg/ml) induced contractions (4 experiments).

Rabbit jejunum:-

In doses ranging between 10 and 30 mg/ml, the extract inhibited the pendular movements and produced dose-dependent relaxation of the tissue (6 experiments). No tachyphalaxis was observed on repeated exposure of the tissue to the same dose of the extract. In two experiments, the extract produced a triphasic response, that is, slight initial relaxation followed by contraction and then profound relaxation. The relaxile effect was not altered by propranolol (0.5 ug/ml; 2 experiments) or phenoxybenzamine (1 ug/ml; 2 experiments) nor by their mixture (3 experiments); also it was not blocked by pentolinium (5 ug/ml; 1 experiment). However, the extract sensitized the tissue to the relaxile effects of adrenaline (0.5 ug/ml; 6 experiments) and isoprenaline (0.3 ug/ml; 2 experiments), in that, it augmented the responses of adrenaline and isoprenaline by about 30 and 40 per cent respectively. But, on the other hand, it antagonized the contractile effects of acetylcholine (1 ug/ml; 3 experiments), carbachol (0.5 ug/ml; 4 experiments) and histamine (7 ug/ml; 4 experiments).

Rat fundus:-

In 2 out of 7 experiments, the extract (10-30 mg/ml) produced slight contraction of its own. However, in the subcontractile doses (1, 3 and 10 mg/ml) on these tissues as also on the remaining 5 tissues, it inhibited the 5-hydroxytryptamine induced contractions by 23.0, 54.2 and 80.3 per cent respectively. At 5 and 10 mg/ml doses, it inhibited the contractions induced by $PGF_1 \propto$ or $F_2 \propto$ by 30.7 and 70.2 per cent respectively. The extract induced inhibition was reversible and could be overcome by increasing the dose of the agonists.

Oestrogenized rat uterus:-

The extract did not exert any direct action of its own on the oestrogenized rat uterus upto a dose of 50 mg/ml (3 experiments). It, however, inhibited the contractions induced by PGE_1 (0.6 ug/ml; 3 experiments) by 20.6, 37.2 and 60.4 per cent at 3, 6 and 10 mg/ml doses respectively. Thus, the antagonism was roughly proportional to the dose of the extract and was quickly reversible.

Guinea pig atria:-

The extract had no effect of its own on this preparation upto a concentration of 1.0 mg/ml of the bath fluid. However, at 5 mg/ml concentration, it produced a positive inotropic and chronotropic effect. At a concentration devoid of any effects on the spontaneous activity (1 mg/ml), the extract reversibly inhibited the positive chronotropic and inotropic effects of histamine (3 ug/ml) by about 80 per cent and that of isoprenaline (0.1 ug/ml) by about 80 percent.

Anti-Anaphylactic effect:

Three weeks after active sensitization, ileal pieces of the sensitized guinea pigs (6 experiments) responded by contraction when challenged with the antigen (egg-white 25% v/v; 0.2 ml). Pieces of the intestine kept in Tyrode solution at 6-8°C for upto 24 hr did not lose sensitivity to the antigen.

The height of contraction induced by the anigen was dose-dependent. The extract markedly reduced the antigen-induced contraction at a dose of 3 to 10 mg/ml. At higher concentrations (30-100 mg/ml), the extract completely abolished the antigen response (5 experiments). Subsequent addition of antigen, after the extract

was washed out, did not elicit any contraction though it remained sensitive to histamine. However, the ileal pieces from the extract-pretreated animals (4 experiments) were as sensitive to the contractile effect of antigen or histamine as were those from the non-treated (control) sensitized animals.

Mediator release from lung tissues:

The quantitative estimation of the amount of spasmogens released anaphylactically or chemically was done by assay on the isolated ileal pieces from nonsensitized guinea pigs. The results are presented in Table I. The amount of spasmogens released chemically under the influence of compound 48/80 (8 observations), *in vitro,* was manifold greater (3.58 ± .14 ug/gm) than the controls (0.43 ± .04 ug/gm; $P < .001$; 10 observations); however, the extract almost completely inhibited (0.53 ± .13 ug/gm) the compound 48/80 - initiated release (8 observations). Curiously, the amount of spasmogens released from the lungs of egg albumin-sensitized animals was significantly ($P < .001$) higher (1.36 ± .11 ug/gm; 8 observations) than the nonsensitized animals (0.43 ± .04 ug/gm).

Exposure of the lung tissues, from the sensitized animals, *in vitro,* to the antigen, resulted in significant ($P < .001$) increase in the spasmogen release (2.78 + .13 ug/gm; 7 observations); however, the extract significantly ($P < .001$) reduced the antigen-initiated release (1.86 + .09 ug/gm; 8 observations). Lung tissues from sensitized animals, fed on the extract during the course of sensitization, when challenged *in vitro,* with antigen also released lower amounts (2.14 ± .11 ug/gm; 5 observations) than those from the nontreated sensitized animals (2.78 ± .13 ug/gm).

In 5 experiments, the contractile effect of spasmogens was studied in the presence of mepyramine. Significant reductions ($P < .05$) in the degree of contractions were observed in mepyraminized tissues. However, still the spasmogens remained markedly effective even in the presence of mepyramine.

Cutaneous hypersensitivity:

In the sensitized animals, intradermal injections of the egg-white, in concentrations ranging from 5 to 25%, produced pronounced effects at the site of injection starting from initial blue discoloration to clear-cut wheal formation (5 experiments). The effect was discernible (±) within 15 minutes; by 30 minutes the intensity of reaction became moderate (++) reaching to highly severe (++++) stage by the second hour after injection (Table II). Thereafter, the severity of reaction gradually declined to milder degree by the 4th hour. However, effect of the antigen was not dose-dependent in that 5,10,15,20 and 25% concentrations of the antigen produced similar degree of response. Local infiltration of the extract strikingly antagonized the antigen response during the entire 4 hour observation period (5 experiments). In the sensitized animals fed with the extract, the antigen produced only mild reaction which was significantly less than that produced in the nontreated animals (3 experiments). The antigen had no effect in the non-sensitized normal animals (2 experiments).

Cutaneous capillary permeability:

In the dose range of 1-10 ug, histamine dihydrocholoride induced marked increase in the permeability (6 experiments). The effect of histamine was roughly proportional to the dose. The extract alone, upto a dose of 100 mg, did not produce any marked increase in the capillary permeability (4 experiments). However, it significantly reduced the histamine-induced increase in the permeability (Table III) and also facilitated the restoration of normalcy (6 experiments). For instance, whereas the effect of 10µg histamine alone persisted until 4 hour of observation period, its effect in the presence of extract was almost negligible at the end of that period. The inhibitory effect of 30 mg extract was comparable to 5-10 µg of mepyramine maleate; at 15 µg, mepyramine completely nullified the histamine effect (4 experiments).

Like histamine, bradykinin and 5-hyroxytryptamine also produced marked increases in the permeability which remained unaltered in the presence of mepyramine (Tablve IV). However, the extract did reduce the effects of both bradykinin and 5-hydroxytryptamine, though the reduction was comparatively lesser than that for histamine (3 experiments).

Oral administration of the extract, 20 gm/kg, daily for one week, also appreciably inhibited the responses of intradermally injected histamine, bradykinin and 5-hydroxytryptamine (2 experiments).

No sign of tissue damage or necrosis was observed at the site of extract injection.

Histamine-induced bronchospasm:

The results are presented in Table V. All the 5 animals in the control group developed breathing difficulty and anoxic convulsions after mean exposure time of 68 seconds to histamine aerosol and then died. At a dose of 20 gm/kg, the extract protected 40 per cent (2 out of 5) animals from developing respiratory distress or convulsions and death; the remaining three animals did develop the convulsions but the latent period of the onset of respiratory distress was significantly longer (128 seconds) than that in the controls (Table V).

At a dose of 5 mg/kg, mepyramine failed to protect the animals against histamine-induced bronchospasm; all the 5 animals developed convulsions after mean exposure time of 64 seconds to histamine aerosol and died. At 15 mg/kg dose, however, mepyramine protected all the 5 animals from developong respiratory distress or convulsions and death (Table V).

Messenteric mast cells:

At a concentration of 10 µg/ml, compound 48/80 produced significant ($P < 0.02$) degree of degranulation ($38.0 \pm 9.84\%$) of messenteric mast cells as compared to those treated with normal saline alone ($4.0 \pm 2.1\%$). The extract completely protected the mast cells from getting degranulated by the compound 48/80 since in the presence of the extract, the compound could induce degranulation only of $4.8 \pm 2.78\%$ cells; this degree of degranulation was almost comparable to that of normal saline (Table VI). Four experiments were conducted in each set.

Carrageenan-induced inflammation:

Intraplanter injection of carrageenan caused significant increase in the paw volume due to oedematous swelling (10 animals). The increases in the paw volume at ½, 1, 2, 3 and 4 hr after carrageenan injection were 24.9, 27.7, 45.2, 73.4 and 67.8% respectively. Oral administration of the extract did not reduce the carrageenan effect. Two doses (20 and 40 gm/kg) of the extract were tested. In the animals receiving 20 gm/kg (8 animals) extract, the per cent increases in the paw volume at respective intervals were found to be 22.0, 26.4, 40.7, 72.6 and 68.4, and in those receiving 40 gm/kg (7 animals) these figures were 30.0, 34.8, 55.1, 68.4 and 81.2. However, brufen did significantly ($P < .001$) inhibit the carrageenan-induced oedema (8 animals), in that, in this group of animals the per cent increases were 9.5, 10.9, 19.7, 9.3 and 9.8.

Cotton pellet-induced granulation tissue formation:

In the control group of animals, the wet and the constant dry weights of the granulation tissue were 137.4 ± 4.21 and 35.3 ± 2.61 mg respectively (10 animals). Oral administration of the extract (20 gm/kg) throughout the one week experimentation period did not reduce the granulation tissue formation (10 animals); the wet and dry weight of the tissue in the extract-treated animals were 133.6 ± 3.84 and 34.7 ± 2.43 respectively. However, dexamethasone (8 animals) and brufen (7 animals) significantly ($P < 0.001$) reduced the granulation

tissue formation; the weights in the respective groups were 56.2 ± 1.63 and 16.8 ± .82, and 74.3 ± 2.03 and 22.5 ± 1.36.

Travel of charcoal meal:

In control group of mice, 64.0 ± 5.68 per cent length of the small intestine was travelled by charcoal (12 animals). The extract (20 gm/kg) had no marked effect on the motility since in the mice (10 animals) receiving extract the distance travelled by charcoal meal (58.5 ± 5.20 per cent) was almost similar to that observed in the controls. However, carbachol markedly increased the per cent distance covered by charcoal (8 animals) which was 74.37 ± 1.99, and this increase was completely, and significantly ($P < .001$), inhibited by the extract (10 animals). The results are presented in Table VII.

Fluid formation in the rat intestinal loop:

Magnesium sulphate solution (2 ml; 15% w/v) produced 5.44 ± 0.17, 5.23 ± 0.46 and 5.38 ± 0.23 ml fluid accumulation at 1, 2 and 3 hours respectively in the ligated intestinal loop of adult rats (5 animals at each interval). The extract (1 gm/loop) did not influence the course or volume of fluid formation. The volumes of fluid recovered from the loops pretreated with extract were 5.29 ± 0.34, 5.58 ± 0.49 and 5.16 ± 0.27 at the respective intervals (6 animals in each group). Almost similar volumes were recovered from the loops of those animals which were fed the extract (10 gm/kg) one hour before ligation of the intestinal loop and injection of magnesium sulphate (6 experiments).

DISCUSSION

The results of the present investigation on the herbal formulation indicate that the crude aqueous extract of the formula exerts antihistaminic effect. However, the term "antihistaminic" is used for convenience and because, as in the previous reports reviewed[27], antagonism to histamine was the first to be detected and studied. The term does not imply the highly specific antihistamine action which characterizes synthetic or classical antihistamines. Nevertheless, in almost all the parameters covered in the present study its effect do suggest of certain degree of specificity against histamine but many more parameters need to be studied in greater details. On the isolated tissue preparations, larger doses of the extract were required for antagonising the effects of acetylcholine, carbachol, 5-hydroxytryptamine, bradykinin, prostaglandins and potassium chloride. This type of wide and varied antagonism is not uncommon to synthetic antihistamines[28] as also to naturally-occurring antihistamines[29,30,31]. The ability of naturally-occurring antihistamines to inhibit the smooth muscle contractions induced by so many agonists and antigen has been described as "the blanket activity"[27]. On the isolated guinea pig ileum and in certain other parameters covered in the present study, histamine manifests its action by acting upon H_1 receptors. The only preparation having H_2 receptors used in the present investigation was isolated guinea pig atria[32]. On this preparation, the extract inhibited the effect of both histamine and isoprenaline indicating a nonspecific effect on H_2 receptors. Nonetheless, it would be advisable, before arriving at such a conclusion, to conduct additional experiments envolving H_2 receptors particularly the Shay rat preparation. Synthetic antihistamines do not block the action of histamine on the gastric acid secreting glands; indeed, this anamalous situation has led to the concept that histamine receptors on these glands are different from those on the intestinal smooth muscle[33]. It may be interesting to note that naturally-occurring anti-histamines from human and horse urine[34] and from frog skin[31] inhibit histamine-induced gastric acid secretion in mammals. Need for such a study is emphasized here particularly because of the fact that the decoction of the formula is recommended to be drunk preferably in the empty stomach.

Catecholamines, like adrenaline and isoprenaline do inhibit the spasmogenic action of histamine and other agonists on the isolated smooth muscle preparations. On the rabbit jejunum, like adrenaline and

isoprenaline, the extract produced a relaxile effect; however, this effect was not blocked by propranolol or phenoxybenzamine nor by their combination indicating thereby that the relaxile effect was not mediated through the activation of adrenergic receptors. Also, the extract-induced relaxation did not exhibit any degree of tachyphylaxis. These findings therefore suggest that the relaxant effect of the extract is probably due to its direct action on the relaxile elements of the smooth muscle independent of the involvement of the adrenergic receptors or catecholamine stores. These findings, render it unlikely that the antihistaminic principle in the extract is ephedrine or ephedrine-like. Moreover, the extract itself antagonised, at certain dose level, the effect of isoprenaline, as it did of histamine, on the isolated guinea pig atria.

However, the smooth muscle relaxant activity of the extract as observed on the rabbit jejunum is an interesting finding. Antagonism of certain agonists on the rabbit jejunum as also on depolarized ileum further strengthens the view that it acts directly on the relaxile elements.

The non-specific spasmolytic agents such as papaverine and polysorbates inhibit isolated guinea pig ileum contractions induced by diverse agonists including potassium chloride[35] which induces contraction by surface depolarization. In this respect, they completely resemble the extract. Therefore, it is reasonable to propose that in a normal isolated guinea pig ileum, the extract inhibits certain agonists by some mechanism at the cell membrane of the smooth muscles. On the other hand, in the isolated guinea pig ileum depolarized by prolonged exposure to excess potassium sulphate, the cell membrane is depolarized and non-functional and, agents like calcium chloride which induce contraction in this preparation do so by directly acting on the contractile elements[36,37] inside the cell by initiating the excitation-contraction-coupling mechanism[38]. This calcium chloride-induced contraction is blocked by papaverine[35] as also by the extract. This finding suggests that, at the intracellular sites of excitation-contraction-coupling, the extract reduces the availability of calcium. All these findings may also explain the clinically conspicuous antispasmodic action of the extract.

Like isoprenaline, the extract produced a positive inotropic and chronotropic effect on the isolated atrial preparations of guinea pigs. The nature of cardiac stimulant action of the extract is not clear since in substimulent doses it inhibited the stimulatory effects of both isoprenaline and histamine. This action needs further study.

Active anaphylaxis in the guinea pig was used in this study to find out the scientific basis for the clinically observed anti-asthmatic effect of the formula. There is a whole series of events in the anaphylactic reaction, starting with the production of reaginic (type of) antibodies and cluminating in the actual smooth muscle contraction[39]. A Schultz-Dale reaction is the contractile response of the sensitized smooth muscle preparation, *in vitro*, when challenged with antigen. In the present study, the extract effectively antagonized the antigen-induced contraction (Schultz-Dale reaction) of the ileal pieces of sensitized guinea pig. However, systemic (oral administration) of the extract through the course of sensitization period was not effective in that the ileal pieces from extract-fed, sensitized animals reacted adequately to the antigen. This finding, therefore, suggests that, in the doses used, the extract does not affect the generation/production of specific antibodies or their concentration in the target organs but interferes with the interaction of these antibodies with the antigen and thereby prevents the acute anaphylactic shock. The tissues once exposed to the extract and then challenged to the antigen remained unresponsive to subsequent addition of the antigen evenafter the extract was washed out; this finding suggests that neutralization of the antibodies was complete and total.

The lung is the target organ in asthma. Therefore, the release of mediators of anaphylaxis from this organ was studied. The reduction in the amount of spasmogens released from the lungs, as observed in the present study, shows the effect of the plant materials on the target organ. The degree of contractions recorded, as presented in Table I, are most likely to be due to histamine release because of the shorter time course of the contractions which indicates that histamine is the major spasmogen released. The reduction in the total

content of spasmogen as a result of the *in vitro* treatment with the extract is of significance, and so is the reduction in the amount of the amine released anaphylactically. With respect to the effects of histamine the basic difference between normal and hypersensitive individuals is the quantity of the released mediators which will elicit a pathological response. The same quantity will be innocuous in normal individuals and pathological for hypersensitive individuals. A mechanism for the reduction in the amount of mediators released either by decreasing the total content or by interfering with the release mechanism is of special significance as this would tend to correct the underlying derangement in the hypersensitive individual by decreasing the amount of meditors released to a level below the pathological level. The extract appears to affect both mechanisms of reduction, so that its effect is not only at the step of smooth muscle contraction but also at a step preceding the release of mediators.

The contractions recorded as a result of mediators released from the lung tissue in the presence of mepyramine show that the extract has effect also on the release of spasmogens other than histamine. The significance of this result lies in the fact that in man the release of spasmogens other than histamine is important in asthmatic attacks[40]. Histamine is known to be formed during the sensitization period and merely released on challenge[41], whereas the other mediators are known to be made *de novo* in response to the challenge[42]. The effects of the extract on the levels or effects of these mediators of anaphylaxis also indicate its active interference in the response to challenge. It would seem that the extract affects several steps in the sequence of events in anaphylaxis, and this could account for its prophylactic use in asthmatics.

Further, the extract also reduced the level of histamine release from the lungs exposed *in vitro* to compound 48/80. This compound acts like antigen at the cell surface, as suggested by their affinity for acid mucopolysaccharides present in the membrane[43], or the essential component of their action may be a mobilization of cellular calcium[44]. Our experiments on the isolated depolarized tissues have indicated that the extract might be interfering with the calcium-interaction with the cell membrane. It is likely that the effect of extract observed on the compound 48/80-induced release might as well be due to its action on the mobilization of cellular calcium.

In the present study, the extract inhibited the effect of compound 48/80 on the mast cells. Compound 48/80 is a potent degranulator of mast cells which contain besides histamine many other pharmacologically-active substances. These cells supposedly play a pivotal role in the causation of asthma or bronchitis because of their ability to produce and release mediators of broncho-constriction[45]. Therefore, the mast cell stabilizers have been considered effective in the prophylaxis of asthma. One of the outstanding examples is disodium cromoglycate, which is a unique drug that has no bronchodilator properties; it rather prevents bronchospasm probably by stabilizing mast cells so that release of preformed mediators by antigen-antibody reaction or other stimuli is inhibited[46]. An inhibitory action on antigen-induced production of histamine and SRS-A has been demonstrated in peritoneal mast cells *in vivo* and *in vitro*[47]. However, the action of suppressing histamine release is not a general one; histamine release from mast cells in response to releasing drugs such as compound 48/80 or bee venom is unaffected[48]. And, in this respect, the extract of the formula defers with sodium cromoglycate since the extract prevented the release induced by compound 48/80 and also exhibited smooth muscle relaxant and bronchodilator properties. It would be interesting to study the effect of extract on antigen-induced degranulation of mast cells because eventhough histamine has been repeatedly identified as a prominent constituent of mast cells and is released in large quantities following antigen-antibody interaction[49], histamine is thought to be of relatively little importance due to the presence of other mediators[50]. Apparently, mast cells stabilizing effect of the extract does not appear to be nonspecific since it failed to produce stabilization of fresh red blood cells[51].

In the present study, a simple model for studying the cutaneous hypersensitivity response has been followed. This does not involve the sensitization procedures in which the antigen was presented either in an

unusal physical state (e.g. adsorbed on aluminium hydroxide gel) or in conjuction with certain adjuvant toxins (e.g. *B. pertussis*) nor when the animal body was subjected to particulr stresses so that the corticosteroid levels were temporarily degraned[52]. In our experiments, the guinea pigs were simply sensitized by the intraperitioneal injection of egg-white and were used for test 3 weeks after sensitization. In the sensitized animals, the intradermal infiltration of the antigen produced a pronounced effect which appeared to be specific because in the non-sensitized (normal) guinea pigs, the antigen failed to induce wheal formation. The extract, when injected locally prior to the injection of antigen at the same site, completely antagonized the wheal formation by the antigen. However, oral administration of the extract was relatively less effective in antagonizing the effect of antigen. This could be due to lower concentration of the extract reaching the cutaneous tissues as compared to its local injection.

Th extract also inhibited the increase in cutaneous capillary permeability induced by histamine, bradykinin and 5-hydroxytryptamine. However, its effect against histamine-induced increase in permeability was more marked than that induced by bradykinin and 5-hydroxytryptamine suggesting greater affinity for histamine receptors than those for the remaining agonists. In the dose which blocked the histamine response, mepyramine had no inhibitory action against bradykinin and 5-hydroxytryptamine. Thus, in this respect, the extract exerted a wider range of activity against these agonists than mepyramine maleate. The antagonism of the increase in cutaneous capillary permeability as also of cutaneous hypersensitivity does not appear to be the nonspecific effect of extract on membrane permeability since in the rat intestinal loop experiment, it failed to affect the magnesium sulphate induced fluid accumulation which results from the altered permeability of intestinal mucosa due to osmotic tension.

The extract increased the latent period of histamine aerosol-induced anoxic convulsions and protected certain percent of animals from death. Bronchial muscle of guineapigs is exquisitely sensitive to histamine and bronchoconstriction leads to death. In clinical situation, altered reactivity of bronchial musculature triggers acute bronchospasm. Therefore, any drug or agent which can inhibit the histamine induced bronchospasm could be of promising value in the treatment of acute asthmatic attacks. The constrictor action of histamine on respiratory smooth muscle is mediated through H_1 receptors. H_1 receptor blocker mepyramine maleate did protect the histamine-induced bronchospasm and the resultant death but at a large dose of 15 mg/kg. In clinical practice also, several investigators have reported some beneficial effects with doses of antihistamines higher than those used for allergic rhinitis[53,54]; these effects were particularly noticeable when antihistamine was given intravenously[55]. However, the extract offered the observed protection (40%) at the usual experimental dose-level. It would be interesting to study the effect of higher doses of the extract for it may offer still better degree of protection.

In the doses used, the extract did not produce any significant degree of suppression of the oedemagenic action of carrageenan in the rat hind limb paw nor of granulation tissue formation around the subcutaneously implanted cotton pellets. Apparently, therefore, the extract was devoid of antiinflammatory effect since the classical antiinflammatory agents, both of steroidal and nonsteroidal nature, antagonize the inflammation in these experimental models[56]. Caution is, however, required in the intrepretation of the results of experimental study regarding the devoidance of antiinflammatory effect of the extract to the clinical situation; the type of inflammation in the tracheobronchial musculature in patients might be of a different type than experimentally produced in the present study. Other models of inflammation need to be investigated.

Carrageenan induced oedema formation is mediated through the release of various mediators, locally, at the site of carrageenan injection in a sequential manner[57]. It is curious to note that though the extract effectively antagonized the release of mediators of anaphylaxis induced by the antigen from the sensitized lung and of histamine by compound 48/80 from the non-sensitized lung, it failed to alter the carrageenan-induced release of mediators of inflammation. This finding suggests that the extract exerts a specific effect on

the release process in the bronchial tissue. It is, therefore, not unlikely that the extract might as well have some specific effect on the inflammatory process in the tracheobronchial system.

Oral administration of the extract did not produce any marked effect on the gastrointestinal motility as was observed by the travel rate of charcoal meal in mice. However, it significantly inhibited the carbachol-induced increase in the gastrointestinal motility. This finding, coupled with its effects on the isolated guinea pig ileum and rabbit jejunum, do suggest that the extract possesses some anticholinergic effects. The maintenance of mild degree of airway tone in animals and man is mediated by parasympathetic cholinergic nerves[58,59]. Furthermore, inhalation of irritants will provoke bronchoconstriction in susceptible individuals which can be prevented by the prior administration of anticholinergic drug atropine and, accordingly, the role of parasympathetic nervous system in the maintenance of chronic airway obstruction has been emphasized[60]. At least part of the chronic airway obstruction in many perenially asthmatic children is a consequence of parasympathetically mediated bronchospasm[61]. It is, therefore, likely that the extract by exerting anticholinergic action, besides many diverse type of actions as discussed above, might produce a complimentary effect in irritants-provoked bronchoconstriction and, to some extent, in parasympathetically mediated chronic airway obstruction.

Altogether, the results of the present study may help to establish a scientific basis for the use of these plants, in crude form, in the diseases of tracheobronchial system or chronic airway obstruction. Briefly, the above mentioned findings suggest that the extract produces its beneficial effects by (i) exerting antihistaminic effect, (ii) causing smooth muscle relaxation, (iii) preventing the release of pharmacologically-active substances both under immunological and non-immunological conditions, (iv) inhibiting the antigen-antibody interaction, (v) preventing the hypersensitivity response, (vi) causing mast cell stabilization, (vii) reducing the histamine aerosol-induced bronchospasm, (viii) inhibiting the increase in capillary permeability and (ix) exerting alluded anticholinergic action.

SUMMARY

The crude aqueous extract of a herbal formula composed of nine plant ingredients, namely- dried fruits of *Vitis vinifera, Zizyphus vulgaris, Cordia latifolia, Malva sylvestris,* seeds of *Althaea officinalis,* rhizome of *Glycyrrhiza glabra,* whole plants of *Lavandula stoechas* and *Adiantum capillus veneris* and flowers of *Viola odorata,* has been found to antagonise, in smaller doses, the spasmogenic effect of histamine, and, in larger doses, that of the other agonists on the isolated guinea pig ileum and of calcium chloride on the depolarized tissue. On rabbit jejunum, it produced relaxation and augmented the responses of isoprenaline and adrenaline. It inhibited the spasmogenic effects 5-hydroxytryptamine and $PGF_1 \propto$ and $F_2 \propto$ on the rat fundus and of PGE_1 on rat uterus. It stimulated the guinea pig atria but in substimulant doses antagonized the effects of isoprenaline and histamine. It inhibited the Schultz-Dale reaction, reduced the release of pharmacologically-active substances from the lungs induced by the antigen or compound 48/80, appreciably stabilized the mast cells, inhibited the cutaneous hypersensitivity response as also the increase in cutaneous capillary permeability induced by histamine, 5-hydroxytryptamine and bradykinin, markedly suppressed the histamine aerosol-induced bronchospasm and inhibited the carbachol-induced increase in gastrointestinal motility. These findings convincingly support the clinical usefulness of these plants in the treatment of bronchial asthma and chronic bronchitis.

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TABLE I: EFFECT OF THE EXTRACT ON THE RELEASE OF MEDIATOR(S) FROM THE LUNG TISSUE, INDUCED BY COMPOUND 48/80 OR ANTIGEN, CALCULATED IN TERMS OF HISTAMINE (ug/gm).

Tissue	Mediators concentration Mean ± S.E.
Control lung from nonsensitized animal	0.43 ± 0.4
Lung from nonsensitized animal exposed to compound 48/80	3.58 ± .14
Lung from nonsensitized animal first exposed to the extract and then to compound 48/80	0.53 ± .13
Control lung from sensitized animal	1.36 ± .11
Lung from sensitized animal exposed to antigen	2.78 ± .13
Lung from sensitized animal first exposed to the extract and then to the antigen	1.86 ± .09

TABLE II: EFFECT OF THE EXTRACT ON ANTIGEN-INDUCED CUTANEOUS HYPERSENSITIVITY RESPONSE IN PARTIALLY ANAESTHETIZED GUINEA PIGS. THE ANIMALS WERE SENSITIZED WITH EGG WHITE 3-4 WEEKS BEFORE THE EXPERIMENT.

Drugs	Time in Hours					
	¼	½	1	2	3	4
Normal saline	–	–	–	–	–	–
Egg albumin 5%	±	++	+++±	++++	+++	+±
Extract 100 mg	–	–	–	–	–	–
Extract 100 mg + Egg albumin 5%	–	–	–	–	–	–
Egg albumin 5% in extract-fed animal	–	–	±	+±	±	–

TABLE III: EFFECT OF THE EXTRACT AND MEPYRAMINE MALEATE ON THE INCREASE IN CUTANEOUS CAPILLARY PERMEABILITY INDUCED BY HISTAMINE.

Drugs	Time in Hours					
	¼	½	1	2	3	4
Normal saline	−	−	−	−	−	−
Histamine 1 μg	±	++	++±	+±	+±	±
Histamine 3 μg	++	+++	+++	+++	++	+
Histamine 10 μg	++	+++	++++	++++	+++	++±
Extract 30 mg	−	±	±	−	−	−
Extract 30 mg + Histamine 1 μg	−	±	+	+	±	−
Extract 30 mg + Histamine 3 μg	−	+	+±	+	+	−
Extract 30 mg + Histamine 10 μg	−	+	+±	+±	+	±
Mepyramine 5 μg + Histamine 10 μg	−	++	+±	+	−	−
Mepyramine 10 μg + Histamine 10 μg	−	+	+	±	−	−
Mepyramine 15 μg + Histamine 10 μg	−	−	−	−	−	−

TABLE IV: EFFECT OF THE EXTRACT AND MEPYRAMINE MALEATE ON THE INCREASE IN CUTANEOUS CAPILLARY PERMEABILITY INDUCED BY BRADYKININ AND 5-HYDROXYTRYPTAMINE.

Drugs	Time in Hours					
	¼	½	1	2	3	4
Normal saline	–	–	–	–	–	–
Bradykinin 1 μg	++	++++	++++	++++	+++±	+++
Extract 30 mg	–	–	–	–	–	–
Extract 30 mg + Bradykinin 1 μg	–	++	++	++	++	+±
Mepyramine 15 μg + Bradykinin 1 μg	++±	++++	++++	++++	++++	+++
5-HT 1 μg	+	+++	++++	++++	++++	++++
Extract 30 mg + 5 HT - 1 μg	+	++	++	++±	++	+
Mepyramine 15 μg + 5 HT 1 μg	+	+++	++++	++++	+++±	+++±

TABLE V: EFFECT OF THE EXTRACT AND MEPYRAMINE ON HISTAMINE AEROSOL - INDUCED BRONCHOSPASM IN GUINEA PIGS.

Group	Onset of convulsions in seconds	Number of animals died / Number of animals in the group	Per cent mortality
Control	68	5/5	100
Mepyramine 5 mg/kg	64	5/5	100
Mepyramine 15 mg/kg	No convulsion	0/5	0.0
Extract 20 gm/kg	128*	2/5	40

* Mean of three animals only.

TABLE VI: EFFECT OF THE EXTRACT ON MAST CELLS DEGRANULATION INDUCED BY COMPOUND 48/80.

Drugs	Per cent degranulation Mean ± S.E.	P value
Normal saline	4.0 ± 2.1	
C 48/80 10 μg/ml	38.0 ± 9.84	< 0.02
Extract 10 mg/ml + C 48/80 10 μg/ml	4.8 ± 2.78	

TABLE VII: EFFECT OF THE EXTRACT ON THE INTESTINAL MOTILITY OF MICE AS ASSESSED BY THE TRAVEL OF CHARCOAL MEAL.

Drugs	Dose/kg	Mean ± S.E. per cent length of small intestine travelled by charcoal meal
Distilled water	10 ml	64.0 ± 5.68
Extract, oral	10 gm	58.50 ± 5.20
Carbachol, i.p.	50 μg	74.37 ± 1.99
		P < .001
Extract, oral + Carbachol, i.p.	10 gm + 50 μg	59.0 ± 2.32

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EFFECT OF CERTAIN MEDICINAL PLANTS CLINICALLY USED IN RHEUMATOID ARTHRITIS ON EXPERIMENTALLY INDUCED ULCERS

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Abstract

Earlier studies revealed that an aqueous extract of a herbal formulation (RA) consisting of dried roots of *Withania somnifera* Linn, rhizome of *Alpinia galanga* Wild, corm of *Merendra persica* Linn and roots of *Pyrethrum indicum* DC exhibited significant anti-inflammatory activity in various experimental inflammatory models and was also devoid of any teratogenic and mutagenic potentials in mice. The present study was designed to investigate the effect of RA extract on experimentally induced ulcers in laboratory animals. Acute and chronic oral treatment of RA extract upto a period of 1 to 5 months in the dose levels of 400 and 800 mg/rat/day along with the drinking water (20 and 40 mg/ml) did not exhibit any abnormality both in the cardiac and pyloric portion of the stomach in Albino rats of either sex compared to controls. RA extract (0.5 g/kg) exhibited protection against the ulcers induced by pyloric ligation. The percentage reduction in ulcer score compared to control was 45.6 ($P < 0.002$). There was a significant ($P < 0.03$) reduction in all the parameters such as total volume (36.6%) and total (36.8%) and free acid (42.6%) as compared to control. RA extract 0.5 g/kg, 1.0 g/kg and cimitidine 200 mg/kg were also tested for their effect on stress induced water restraint gastric lesions; RA extract (0.5 g/kg and 1.0 g/kg) significantly ($P < 0.01$) prevented gastric lesions induced by non-steroidal anti-inflammatory agent (indomethacin, 10 mg/kg); the effect was comparable to that of cimitidine 10 mg/kg.

INTRODUCTION

At the Islamic Centre for Medical Sciences (Ministry of Public Health), Kuwait, a herbal formulation (RA) consisting of dried roots of *Withania somnifera* Linn, rhizome of *Alphinia galanga* Wild, corn of *Merendra persica* Linn and roots of *Pyrethrum indicum* DC is successfully being used clinically in the treatment of rheumatoid arthritis. These four plants have been recommended [1-5] for the treatment of rheumatism, sexual debility, diseases of liver and spleen, constipation and as a digestant and carminative. A combination of these plants has been reported[6] to be effective in the treatment of clinical arthropathies. Earlier studies on RA extract indicated significant anti-inflammatory activity using various experimental models[7] and was also devoid of any teratogenic and mutagenic potentials in mice[8]. Recent work[9] showed some functional and behavioural developmental changes in offsprings born to pregnant rats fed with RA extract during pregnancy and lactation period. The roots of *Withania somnifera* has been reported to reduce gastric ulceration and acid production[10]. Gastro-intestinal ulceration is a widely reported toxicological effect of steroidal and non-steroidal anti-inflammatory drugs. The present study was undertaken to investigate the acute and chronic effects of RA extract on gastric mucosa of normal animals. The effect of the extract was also studied in experimentally induced ulcers in laboratory animals.

MATERIALS AND METHODS

Preparation of RA extract:

The four plant materials namely the dried root of *Withania somnifera* (50 gm), rhizome of *Alpinia galanga* Wild (25 gm), corm of *Merendra persica* Linn. (25 gm) and roots of *Pyrethrum indicum* DC (25 gm), were finely powered and mixed. Every 125 gm of RA powder was extracted with 2.5 litres of Sorensen buffer (KH_2PO_4 and Na_2HPO_4 1/15 M; pH 7.5) at 37°C for 5 hours. During this process, the mixture was stirred continuously with the help of an electrical stirrer. The supernatant was filtered through Whatman No. 1 filter paper and stored at 4°C and used within one week.

Evaluation of gastrointestinal toxicity in normal rats:

RA extract was orally administered for a period of 1 to 5 months to groups of Wistar Albino rats of either sex (3 months old, 200-250 g) at a dose level of 400 and 800 mg/rat per day along with drinking water (20 and 40 mg/ml). The animals were sacrificed and the stomach was examined for the presence of ulceration and visually scored in arbitary units of 0-4 according to the severity[11] and compared with the controls. The scoring units are as follows:-

0 = Normal
1 = Scattered haemorrhagic spots and hyperemia.
2 = Deeper haemorrhagic spots and some ulcers.
3 = Haemorrhagic spots and well formed ulcers.
4 = Extensive haemorrhage, ulcers and perforation.

Anti-ulcer studies in Shay rats:

The method developed by Shay *et al*[12] has been widely used to test anti-ulcer activity. Two groups (13 each) of Wistar albino rats (200-250 g) were fasted for 36 hours but allowed drinking water *ad libitum*. One hour before the pyloric ligation, group I animals were treated with vehicle and served as control.

Group II animals were given RA extract (0.5 g/kg) orally by gavage. The animals were anaesthetised with ether. Under aseptic conditions, a midline incision (1 cm) was made below the Xiphoid process and extended downwards. After cutting through the muscle layer, through the linea alba, the stomach was exposed and the pylorus was ligated with a cotton thread. The cut ends of the muscle layer and skin was then sutured. The animals were sacrificed after 5 hours and the stomach removed. The stomach contents were collected for estimation of total volume and acids. The stomach was opened along the lesser curvature, mounted on a cork board and ulcers were examined and visually scored in arbitarary units of 0-4 as described earlier[11]. The volume of the gastric content was recorded, and the contents were centrifuged to get a clear supernatant fluid for determination of total and free acid [13]. This was done by titrating one ml of the clear supernatant of the gastric secretion against 0.01 N sodium hydroxide solution, using methyl orange until the red colour changed into yellowish orange and the volume of the alkali added was recorded (free acid). Then 2 drops of phenolphthalein was added and the titration was continued until a definite red tinge reappeared. The total volume of the alkali added was recorded (total acid). If a yellow colour is obtained on adding the methyl orange, it indicates that there is no free acid in the specimen. In that case phenolphthalein is to be added and titrated for total acid content.

Studies on stress—induced gastric lesions in mice:

Groups of male albino mice (30-40 g) were deprived of food for 24 hours and allowed only drinking water *ad libitum*. After the fasting period, animals were divided into 5 groups of 8 to 12 animals each. Groups I and II

were treated with Sorensen buffer, 1ml/100 g orally by gavage whereas groups III and IV were administered RA extract 0.5 and 1.0 g/kg orally respectively. Group V was injected cimitidine 200 mg/kg (Tagamet, SK&F) intraperitioneally. Groups II to V were immobilized in modified stress cages and then immersed to the level of Xiphoid process in water bath with a constant temperature of 37°C for 4 hours[14]. Thereafter all animals were sacrificed. The stomach was excised and examined for the severity of intraluminal bleeding, mucosal damage, shedding of epithelium and discrete ulcers and visually scored (0 to 4).

Indomethacin—induced gastric ulcers:

Indomethacin (Sigma, USA) suspended in 70% propylene glycol in water (1 mg/ml) was administered orally at a dose of 10 mg/kg at 18 and 36 hr after deprivation of food to four groups of female albino rats (200-250 g). Group I, II and III were given orally buffer 1 ml/100 gm, RA extract 0.5 and 1.0 g/kg respectively and group IV was given cimitidine 10 mg/kg (i.p.) at 17 and 35 hours after deprivation of food. (i.e. one hour before indomethacin administration). Three hours after the administration of the second dose of indomethacin all groups of animals were sacrificed, stomach removed and examined for lesions in the corpus of the stomach and visually scored (0 to 4).

Statistical analysis:

The results were subjected to statistical evaluation by using Student's 't' test or chi-square test wherever appropriate.

RESULTS

Evaluation of gastro-intestinal toxicity of RA extract in normal rats:

Acute and chronic administration of RA extract did not produce any notable signs of gastro-intestinal toxicity. It did not exhibit any significant abnormality both in the cardiac and pyloric portion of the stomach such as hyperemia, haemorrhage, gastric mucosal lesions, ulcers etc. There was no change in the structural morphology in the treated groups of either sex compared to control.

Anti-ulcer studies in Shay rats:

The results are presented in Table I. Microscopic examination of the incised stomach of RA extract treated animals (group II) indicated protection against the ulcers induced by pyloric ligation and revealed only scattered areas of hyperemia characteristic of stage I. The mean ulcer score of group I (control) animals was 2.9 ± 0.28 which was reduced significantly ($P < 0.002$) to 1 ± 6 0.24 in group II (treated) animals. In the group I (control) animals the mean secretory volume was 11.29 ± 1.13 ml and this was significantly ($P < 0.03$) reduced to 7.15 ± 1.03 ml (by 36.6%) in the group II (treated) animals. The free and total acid contents of the gastric secretion of the control group were 17.37 ± 2.46 and $22 + 2.85$ mEq/lit respectively which were reduced significantly ($P < 0.03$) to 10.7 ± 1.42 and 13.89 ± 1.83 mEq/lit (38.6 and 42.6%) respectively in the treated group.

Effect on stress—induced gastric lesions in mice:

The results are shown in Table II. The mean ulcer score of the group I animals (unstressed and treated with vehicle) was 0.2 ± 0.02 which was markedly and significantly ($P < 0.001$) increased to 2.3 ± 0.34 in group II animals (stressed and vehicle treated). The mean ulcer score of group III (RA extract, 0.5 g/kg treated) animals was significantly ($P < 0.001$) reduced to 0.1 ± 0.1 when compared to that of group II animals. The mean ulcer score of group V (cimitidine treated) animals were also significantly ($P < 0.001$) reduced to $0.25 \pm$

0.13 compared to that of group II animals. However group IV (RA extract 1.0 g/kg treated) animals exhibited lesser tendency of protection 1.25 ± 0.32 which was not statistically significant.

Effect on indomethacin induced gastric ulcers:

The results are summarised in Table III. Indomethacin induced a mean ulcer score of 2.1 ± 0.14 in group I animals. When indomethacin treated animals were given RA extract, 0.5 and 1.0 g/kg orally to group II and group III respectively, it was found to reduce the mean ulcer score significantly ($P < 0.01$) to 0.64 ± 0.21 and 0.78 ± 0.24. The mean ulcer score of group IV (cimitidine in combination with indomethacin) was also significantly ($P < 0.01$) reduced to 0.57 ± 0.20 compared to that of group I (indomethacin alone).

DISCUSSION

The results of earlier studies[7] indicated that RA extract has significant anti-inflammatory activity in various experimental inflammatory models. This formula is used clinically in the treatment of rheumatoid arthritis at the Islamic Centre for Medical Sciences, Kuwait. One of the most common reasons for rejecting a compound from further consideration, even though it has no major life threatening side effects, is a high incidence of gastrointestinal disturbances[15]. Gastric toxicity of non-steroidal anti-inflammatory agents, in the form of increased acidity and ulcerogenicity is well documented[16]. There seems to exist a relationship between anti-inflammatory potency and ulcerogenic activity of anti-rheumatic drugs[17]. The results of the present studies reveal that RA extract did not induce ulcerogenicty on prolonged oral administration to normal rats. The extract did not produce any abnormality in the gastrointestinal tract and there was no change in the structural morphology in the treated group.

Withania somnifera, a major component of RA extract has been reported to reduce gastric ulceration and acid formation[10]. Therefore, the effect of RA extract on experimentally induced ulcers using Shay rats, stress induced gastric lesions in mice and indomethacin induced ulcers in rats was studied. These models involve various mechanisms in the pathogenesis of ulceration or gastric mucosal damage.

The model developed by Shay *et al* [12] has been used extensively by several workers to test anti-ulcer activity. The rat stomach secretes gastric juice continously at a constant rate. If a 2-6 hour ligation period is used, the effect of a test compound on the volume of gastric juice, acid and pepsin concentration and output can be measured[18]. RA extract exhibited protection against the ulcers induced by pyloric ligation and reduced the ulcer score, total volume and gastric acidity compared to controls in Albino rats (Table I).

Hypothermic restraint stress produces disturbances of gastric mucosal microcirculation[19], alteration in gastric secretion[20] and abnormal motility[21]. The RA extract (0.5 g/kg) indicated a protective effect on gastric lesions in Albino mice which was comparable to that of cimitidine (Table II). The high dose (1.0 g/kg) treated animals exhibited lesser tendency of protection against restraint-induced lesions compared to the optimal dose (0.5 g/kg). It has been reported that the major component of RA extract namely *Withania somnifera* has shown lesser biological activity at higher doses[10]. It has also been observed that very high doses of certain herbal preparations did not show the desired effect as exhibited by the optimal dose[35].

It has been reported that indomethacin causes gastric ulceration[22] and a dose dependent increase of pentagastrin stimulated acid secretion[23]. In the present investigation it was found that RA extract was able to prevent the gastric damage caused by indomethacin (Table III). Hence the possibility of inhibition of pentagastrin by RA extract cannot be ruled out.

It has also been postulated that histamine might play an important role in mediating the gastric secretion stimulated by gastrin, vagal excitation and cholinergic actions in both pylorous ligated Shay rat techniques and stress induced restraint ulcers[24]. It has been reported that stress induces mast cell degranulation and

histamine release in gastric mucosa[25]. A rise in histidine decarboxylase (an enzyme involved in the synthesis of histamine) activity of the stomach was observed and reported[26] in restraint ulcers which lead to the release of histamine from gastric mucosa. The release of histamine during the stress in turn produces damage in the vascularity of mucosa and rupture of histamine dilated capillaries resulting in the production of gastric lesions[27,28]. Our earlier studies[7] revealed that the formulation exhibits significant anti-histaminic activity. Preliminary studies in our laboratory have indicated that RA extract is active in inhibiting the messenteric mast cell degranulation and associated release of histamine induced by compound 48/80. Further, it has been postulated that anti-allergic compounds might prevent the release of histamine by stabilization of mast cell membranes[29,30]. It has been reported recently[31] that RA extract was able to stabilize sheep red blood corpulsles (SRBC) membranes subjected to hypotonic and heat stresses *in vitro.* Hence it is likely that RA extract might prevent the release of histamine from mast cells by stabilizing their membrane system. Further, *Withania somnifera* was also found to stabilize the lysosomal membrane of the rat liver both *in vitro* and *in vivo*[10]. Hence the protective action of RA extract against ulcer formation may be also due to its capacity for the stabilization of lysosomal membrane system.

There are reports on the effect of aspirin-like drugs on platelet aggregation[32,33] and inhibition of prostaglandin synthesis in gastric cells[34], leading to accumulation of precursors of prostaglandins, arachidonic acid which is diverted for hydroperoxide synthesis[35]. The role of inhibition of prostaglandin synthesis by non-steroidal anti-inflammatory agents has been considered in gastric damage[36]. This is one of the mechanism postulated for the gastric ulceration caused by the aspirin-like drugs. It is interesting to note that RA extract was found to inhibit the stable phase of carrageenan induced edema (prostaglandin phase) and also to inhibit the edema induced by local injection of PGE_2 in the rat paw[7]. This demonstrates that RA extract is able to inhibit prostaglandin formation. This might be a parodoxical situation. It has been reported that some of the flavonoidal glycosides inhibit both cyclooxygenase[37] and lipoxygenase[38]. The flavonoids are found to reduce gastric mucosal damage induced by non-steroidal anti-inflammatory agents like asprin, phenylbutazone, indomethacin and ibuprofen[39]. It was reported that a major component of RA extract *Withania somnifera* contains bioflavanoids[40]. *Withania somnifera* is reported to be an anti-inflammatory drug which did not exhibit gastric ulcers on prolonged administration[10]. The preliminary studies (Unpublished data) showed the presence of flavonoidal glycosides in *Merendra persica* (another constituent of RA extract) and in RA extract also. It may be possible that flavonoidal glycosides in RA extract may be able to inhibit both lipoxygenase and cyclooxygenase leading to the beneficial effects of RA extract.

During the course of the experiments, it has been observed that the gastric content in the RA extract treated group in all the animal models were thick and viscid suggestive of increased mucin production which may act as a protective barrier against ulceration and studies on this aspect are to be initiated. It is suggested that the anti-histaminic, anti-secretory, antacid like activity and a protective effect on the gastric mucosa may be responsible for the anti-ulcer action of the formulation.

It is quite interesting to find an anti-inflammatory formula, RA extract possessing anti-ulcerogenic activity. Similar actions have been reported for several other anti-ulcer drugs of plant orgin such as Carbonoxelene sodium[41] synthesised from liquorice roots, xanthones of *Calophylum inophyllum* and *Mesua fera*[42], nimbidin, a principle isolated from *Azadhirachta indica*[43], a flavonoidal glycoside Gossypin[39] and certain flavonoidal glycoside isolated from *Clerodendron inerme*[35]. The studies on the effects of the individual plant components of the RA extract on experimentally induced ulcers is under progress.

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TABLE I: EFFECT OF RA EXTRACT ON SHAY RATS

Group	Treatment	Secretory Volume (ml)[a]	Acidity in mEq/L[a]		Ulcer Score[b]
			Free Acid	Total Acid	
		mean ± s.e.m	mean ± s.e.m	mean ± s.e.m	mean ± s.e.m
I	Control n = 13	11.29 ± 1.13	17.37 ± 2.46	22.00 ± 2.85	2.19 ± 0.28
II	RA extract 0.5 g/kg n = 13	7.15 ± 1.03	10.7 ± 1.42	13.89 ± 1.83	1.0 ± 0.24**
	% inhibition	36.6*	42.6*	36.8*	45.6**

a. Results are compared using Students 't' test
b. Results are compared using chi-square test
* $P < 0.03$; ** $P < 0.002$

TABLE II: EFFECT OF RA EXTRACT ON STRESS INDUCED ULCER IN MICE

Group	Treatment	Dose g/kg	No. of Animals	Ulcer Score Mean ± S.E.M.	P. Value
I	Unstressed control	Vehicle	12	0.2 ± 0.02	—
II	Stressed control	Vehicle	10	2.3 ± 0.34	< 0.001[a]
III	RA extract	0.5	10	0.1 ± 0.10	< 0.001[b]
IV	RA extract	1.0	8	1.25 ± 0.32	N.S[b]
V	Cimitedine	0.2	8	0.25 ± 0.13	< 0.01 [b]

The results are compared using Chi-square test
a : results compared with that of unstressed control
b : results compared with that of stressed control

TABLE III: EFFECT OF RA EXTRACT ON INDOMETHACIN (10 mg/kg) INDUCED ULCER IN RATS

Group	Treatment	Dose g/kg	No. of Animals	Ulcer Score Mean ± S.E.M.	P. Value
I	Indomethacin		10	2.1 ± 0.14	—
II	Indomethacin + RA Extract	0.5	7	0.64 ± 0.21	< 0.01
III	Indomethacin + RA Extract	1.0	7	0.78 ± 0.24	< 0.01
IV	Indomethacin + Cimitidine	0.01	7	0.57 ± 0.20	< 0.01

1. The results were compared with indomethacin treated group using chi-square test.
2. RA extract 0.5 and 1.0 g/kg was given orally and cimitidine intraperitoneally twice, one hour before the oral administration of indomethacin at 18 and 36 hr after deprivation of food.

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ISLAMIC RULES GOVERNING FOOD

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1. INTRODUCTION

Most religions and socio-spiritual systems regulate the selection, mode of preparation and mixing as well as (social) consumption of food by their followers. This is because food plays an important social role in addition to providing nourishment. The exent of the regulatory restrictions varies from complete prohibition of the highly nutritious foods of animal origin to minor restrictions on a few items only. No human society is completely free from food restrictions.

In comparison with many other religious and social systems, Islam can be regarded as relatively liberal in allowing freely the consumption of a wide variety of animal, plant, and other foodstuffs provided they are wholesome, safe and not dedicated to anyone other than Allah. Muslims are, however, urged to exercise moderation in eating.

In traditional Islamic societies, the rules governing food have been reviewed and re-examined many times during the last centuries in order to improve their application under changing conditions and with the appearance of new foods as a result of trade, travel and spread of Islam in new geographical areas. These re-examinations are noticed in books and other publications on Islamic jurisprudence *(Fiqh)* published in different countries at different times[1].

During the last 3 or 4 decades important changes in population re-distribution, developments in food technology, trade and travel have created new situations which require a re-examination of rules governing food. Some of the more important problems which have arisen are as follows:

— Millions of Muslims have moved to non-muslim industrialized societies in search of work and are living among communities with different dietary habits.

— Several countries with mainly muslim populations are importing raw and prepared or semi-prepared foodstuffs from international sources often stocked from non-muslim countries.

— Rapid advances in food technology are taking place in non-muslim industrialized countries using raw materials which may include items prohibited in Islam.

— Genetic improvements in meat producing animals have been more successful in single stomached species (pigs and poultry) than in ruminants (cattle, sheep and goats) with the result that the cost of producing pork and poultry meats has been reduced considerably as compared to other meats, thus making them more popular.

In order to tackle the foregoing problems, several individual scientists and organizations have been working on the juridical, ethical, technological and scientific aspects of food and to develop inspection and laboratory methods to assure compliance of Islamic rules. There has also been some confusion as to what are the essential Islamic requirements concerning, for example, foods of animal origin. Meat exporting countries had been faced with varying demands concerning methods of slaughter by different importing countries. This prompted the Codex Alimentarius Commission (FAO/WHO Food Standards Programme) to ask for a clear statement of these requirements. Following some preliminary work at the FAO/WHO Collaborating Centre for Research and Training in Food Hygiene and Zoonoses at Robert von Ostertag Institute, Berlin (West), the World Health Organization and the Muslim World League jointly convened a meeting of Islamic scholars and food scientists in Jeddah in December 1985. The meeting produced a well documented statement[2] on (a) animal species which is lawful to eat, and (b) Islamic methods of slaughter. It dealt also with international meat trade and problems of muslims living in or visiting non-muslim societies.

The present paper provides a general background to the "Jeddah Report" and attempts to bring out problems in the application of some of its recommendations, in face of the modern food technology developed in non-muslim industrial countries. It covers also other relevant developments since the Jeddah meeting.

2. SOURCES AND BASIC CONCEPTS OF RULES GOVERNING FOOD

The two sources of these rules are the Quran and the sayings and actions of the holy Prophet (ﷺ). Subsequently, learned scholars have interpreted the original rules from time to time to apply them to different conditions of the times and places in which they lived. These interpretations are useful examples of readaptations of the rules to new conditions.

Islamic rules in this field uphold some of the concepts in previous scriptures (e.g. prohibition of swine flesh, carrion and blood in the Old Testament) but provide for easier application by abolishing certain other restrictions. Furthermore, Islam abolished idolatrous practices and offerings of food which were widely prevalent among pre-islamic Arabs and other peoples at that time *(Jahiliya)*. These included dedication of food to idols, sacrifices on altars devoted to deities, superstituous avoidance of certain animals or food grown in some fields. Cruel practices such as cutting off of humps, tails and other organs of living animals for use as food and drinking of blood drawn with canulas was also forbidden.

Some other general concepts[3] of these rules are as follows:

— In principle, all clean and wholesome foods are permitted except for a few items which are expressly forbidden.

— Individuals may not eat certain permitted foods they do not like, but no one has the authority to declare them as forbidden for others.

— In case of extreme necessity (e.g. to save life) a forbidden food may be consumed but this should be limited strictly to getting over the emergency.

— Forbidden items and their derivatives remain forbidden regardless of their quantity or change in their physical or chemical characteristics.

— It is forbidden to use tricks, strategems and other types of deceit to make forbidden items permissible, e.g. by changing the name or appearnace.

— Actions which lead to other forbidden actions are also forbidden. Example: manufacturing alcoholic drinks as well as their sale or giving them as gifts.

— These rules are to be observed by all muslims rich or poor, ruler or the ruled alike, and all over the world.

— As a general rule, muslims can eat the food of the "people of the book", christians and jews, provided it does not contain forbidden ingredients such as pork, carrion and blood that flows out.

— Food known to be harmful to health or dangerous to life is forbidden.

— There is no objection to the mixing of permitted foods, e.g. milk, meat or fish, or consuming them in the same meal.

3. PERMITTED AND FORBIDDEN FOODS

As stated above, there is a general permission to partake of foods provided they are clean and wholesome and not expressly forbidden. The foods ordinarily permitted, however, become unsuitable for consumption if dedicated to anyone other than Allah.

Plant and mineral foods and beverages are permitted, if free from intoxicating and toxic substances such as alcohol. Alcoholic drinks are specially mentioned because of their common and widespread use, but other substances affecting the mind (e.g. opium, cannabis, etc.) are similary prohibited.

Among animal species which can be used as food, non-toxic fish, shellfish and other animals inhabiting the sea and freshwater are freely permitted. This includes amphibious animals with the exception of frogs.

For land animals including domesticated and wild species, reference may be made to the "Jeddah Report" and the comprehensive review of Professor Dr. Abdel Aziz Khayyat (1981) mentioned above[1].

The main prohibitions mentioned in the Quran, as already referred to, include swine flesh (all edible tissues and their derivatives), blood that flows out and carrion. The latter would include also animals dying of strangulation, fatally beaten, falling from a height, gored by horns of another animal or torn by wild beasts. Such injured animals would be permitted if slaughtered while still alive, albeit *in extremis.* Animals dedicated to idols or slaughtered by non-believers are also forbidden. In addition, most scholars traditionally extend the prohibition to carnivorous animals and birds, to vermin (rats, snakes, scorpions, cockroaches) and to donkeys and mules, and some also to elephants.

It may be mentioned that certain insects, notably locusts and related grasshoppers are permitted. Honey is prized as a health promoting food.

4. HUMANE CONSIDERATIONS

Islamic rules lay particular emphasis on humane treatment of animals before and during slaughter and require that the process of immolation be as painless as possible. In an earlier paper the present writer[4] referred to the traditions on this subject and to scientific observations to show that the section of large blood vessels of the neck with a sharp knife causes anaemia of the brain of the animal and fall in the pressure of the spinal fluid in a few seconds. Thus the animal is rapidly rendered unconcious and unable to feel any pain.

However, many industrial countries have enacted legislation making it obligatory to stun the animal before slaughter. Some of these countries have substantial muslim minorities among their populations and others export meat to muslim countries. The Jeddah meeting therefore, examined the use of pre-slaughter stunning in the light of Islamic concepts. The scholars were of the opinion that stunning with carbon dioxide and with the bolt-shot pistol were unacceptable especially for sheep. (It seems, they considered these methods to be cruel and inhumane.) The meat of animals stunned with a bolt-shot pistol would however be lawfully permitted if the animal is slaughtered while it is still alive.

Concerning electric stunning, the meeting concluded that "pre-slaughter stunning by electric shock, if proven to lessen the animal's suffering, is lawful, provided that it is carried out with the weakest electric current that directly renders the animal unconcious, and that it neither leads to the animal's death nor renders its meat harmful to consumers". A committee was appointed to study this method of stunning for the foregoing characteristics.

This committee met in Berlin (West) in summer 1986 and observed[5] the method and examined experimental work done on various aspects of its use in the laboratory and in practice. The group concluded that the method was non-fatal[6] and rapidly induced unconciousness during which the animal could be slaughtered painlessly. There was no evidence of untoward changes in the meat which would affect the consumer. There was only one aspect of the procedure on which the committee asked for further evidence before finally recommending its use in Islamic slaughter. This concerned the question of the electric shock itself being painful before the onset of unconciousness.

A WHO consultant - Professor Mohammad Abdul Moneim Abul Fadl - has made further inquiries on this subject. It seems that his work and the fact that electric shock used as therapy for certain mental illnesses in man is not particularly painful, may satisfy the committee on this score. One can, therefore, expect that electric stunning will become generally acceptable as a method of pre-slaughter stunning in Islamic countries. In fact, in some countries, the Muftis have already issued *fatwas* (decisions) in this sense.

As already stated, an important humane provision in Islamic food rules is the prohibition of excising parts of the bodies of living animals (humps, tails) and drawing of blood for use as food and drink.

5. PROBLEMS OF MUSLIMS LIVING IN NON-MUSLIM COUNTRIES

The transport revolution of post-war years has made it easy for people to move over long distances in a short time. This, coupled with the increased need for manpower in industrialized countries which could not be met locally, has led to large migrations of guest workers many of who are muslims. Although the present economic slump has practically stopped further migration, there is a sufficient number already established there to make muslims an important minority. In fact, in Western Europe, the muslims are now the second largest religious group and are estimated to number between 5 and 6 million. In addition, up to one million visit Europe and America every year as tourists, students, temporary workers, businessmen or officials. In the United States, there are around 8 million muslims as estimated by the Islamic Cultural Centre, Washington, DC[7].

The Jeddah meeting recommended two lines of action for muslims resident in non-muslim areas: (a) to seek permission of the authorities to slaughter animals according to Islamic rules. Where this is not possible, (b) to obtain meat of permitted animals slaughtered by people of the book (christians and jews). Foods prepared from such meat may be consumed after ascertaining that they are free from ingredients which may render them forbidden (like pigmeat, blood, carrion, alcohol, etc.).

To take the example of muslims in Western Europe, they have been experiencing difficulties in pursuing both lines of action. The majority of muslims in this area are guest workers often living as migrants having no political weight (voting rights, representation in governing bodies). There are a few exceptions, but there also they are relatively weak politically. Occasionally they have been permitted to slaughter animals separately on the basis of laws granting freedom to practice religion. By and large, such permission has not been forthcoming.

The second recommendation which requires identification and avoidance of foods with prohibited ingredients has proved even more difficult. It will be seen from the following section that even apparently

vegetable or milk products like bread, pastries, biscuits, chocolates, ice cream, cheeses, and margarine, may contain prohibited components, to say nothing of (poultry or calf) sausages, corned beef, soups and other similar foods. The food laws in many countries require that food labels should indicate the main components, but the actual practice of labelling does not take Islamic rules into consideration. For example, components declared as "animal fat", "edible fat", "gelatin", "emulsifier" may have been derived from prohibited raw materials. Many food products such as breads and other bakery products may not carry composition labels at all. Thus it is virtually impossible for the average muslim consumer to be sure that the apparently permitted food offered in the shops is really free from prohibited ingredients.

Among efforts to help the muslim consumers in selecting acceptable foods in the American market, the Islamic Food and Nutrition Council of America (Chicago III.) publishes lists of brands of common food items which are free from prohibited ingredients. In Europe, special shops and enterprises selling acceptable (and ethnic) food items exist in areas where large numbers of muslims are living. These measures are still restricted an do not solve the problems of those who have to eat in canteens or common kitchens at the work place.

6. COMPOSITION OF PREPARED AND PARTLY PREPARED FOODS

The components of mixed, raw or partly processed foods of animal origin can often be identified as to the animal species from which they are derived by chemical, microscopic, immunological or anatomical examination of flesh, blood (non-denatured), fat or bones. Sometimes animal hair found as contaminants can provide a clue to the animal species of origin. Unfortunately, the technogical advances of the last few decades have made it more and more difficult and restricted the possibilities of identifying the animal species of origin. Modern processing of foods currently marketed in western countries uses complex and sophisticated methods of physical and chemical treatment which alter the raw materials beyond recognition even by laboratory analysis. Moreover, some apparently primary ingredients may also have been subjected to processing which may have used religiously prohibited material. For example, cooking oil labelled as "pure vegetable oil" may have been treated with stearates or diglycerides derived from swine tissues.

There are several "functional" and other materials used by the food industry, which could be derived from prohibited (swine tissues or shed blood) or permitted (ruminants, plants) sources. Under western food laws, it is not obligatory to declare the exact origin of these substances on food labels. Following are some of the materials in question[8]:

(a) Gelatin and other thickening materials. Edible gelatin is cooked collagen and is derived from bones and skin parings of slaughtered animals (cattle, pigs and others). Often the materials from different animals are not processed separately and may be imported from abroad, thus making their origin even more obscure. Gelatin is widely used for preparing soups, meats, pastries, ice creams, etc. Alternative thickening and firming materials of vegetable origin such as pectin, agar and alginate would of course be acceptable along with gelatin from permitted animals.

(b) Rennin used as milk coagulant for preparing cheese may be obtained from calf or pig stomachs. The source of rennin is identifiable only if the manufacturer declares it. Acids formed by bacteria are widely used for curdling and cheese making. These are quite acceptable.

(c) Emulsifiers such as mono- and diglycerides, polysorbates and monostearates may be derived from plant or animal (pig, cattle) sources.

(d) Animal fats, notably lard, or their derivatives are widely used in preparing a variety of otherwise acceptable foods such as bread, dough, cakes, pastries and biscuits, poultry and calf sausages, soups and sauces, chocolates, margarines and many other foodstuffs. Some of these foods may also contain

other ingredients of animal origin such as cysteine and emulsifiers. Animal fats are also used for deep frying or simply as pan grease in roasting.

(e) Blood used in blood sausages is readily identifiable but plasma and some other derivatives which are widely used in many food items are not so readily perceived by the consumer.

(f) Alcohol is detectable by the consumer when strong liquors are used as filling in sweets or added to drinks but not easily perceptible if used as "flavour" in small quantities in desserts and other foods.

The foregoing examples show how difficult it is for the muslim consumer to select foods in the western markets which would be free from ingredients derived from prohibited substances. The same difficulty applies to the import of meats and other food products from non-muslim countries. The importers have often insisted on a declaration by exporters (who may or may not be the manufacturers also) that the food imported is free from whatever makes it unacceptable by muslims[9]. The ethical standards of traders and exporters have been found to be variable especially when they know that the truth of their declarations cannot be verified by presently available laboratory methods. Some airlines also put a slip in their meal trays indicating that the meal is free from pork. This declaration may only mean that there is no pigmeat in the meat dish but it does not always mean that the gelatin, emulsifiers, edible fats, stabilizers and other ingredients did not originate in pig tissues or in blood of other animals.

The food industries are tempted to use animal fat as a raw material as it is available in large quantities at reasonable cost. The direct consumption of animal fats has gone down very markedly as a result of the finding that high consumption of saturated fats is a risk factor in cardiovascular disease and cancer of the lower bowel. They are, however, accepted by the people when used in an altered form as food additives or in processing.

7. ORIGIN OF ISLAMIC FOOD RULES

Various hypotheses have been put forward to explain the reasons behind various dietary prohibitions and other food rules. The reasons for some of the rules are clear and others may become clearer with the progress of human knowledge. Some of the reasons as currently understood may be as follows:

(a) Protection and promotion of health. This is the most commonly given reason and is clearly manifest in the following:

- Exhortation to eat clean and wholesome food, but in moderation.
- Avoidance of harmful and toxic food.
- Avoidance of alcohol and other intoxicants.
- Avoidance of carrion and blood that flows out (because of their greater liability to deteriorate and carry harmful contaminants).

(b) Extension of anti-idolatory measures into food rules which prohibit the consumption of food dedicated to idols and to anyone other than Allah.

(c) Avoidance of fraternization and close social mixing with non-believers, apostates and others who may exert undesirable influences on believers.

Other hypotheses with special reference to the avoidance of pork have been listed in an earlier paper by the writer[10]. There is some evidence to show that there may be a positive corelation between liver cirrhosis and consumption of pork[11].

Much has been written[12] on food laws in the Old Testament some of which may be relevant to the subject of the present paper as some of the Islamic food rules confirm the prohibitions in earlier scriptures.

8. CONCLUDING REMARKS

A restatement of the Islamic rules governing food shows that they are simple and clear and can be applied easily in muslim communities. Some problems are, however, created by developments in food industries in the western diaspora where millions of muslims are now residing. The industries there make frequent use of prohibited raw materials or their derivatives which are not necessarily mentioned on food labels.

Following approaches have been proposed to meet the difficult situation in the western diaspora:

(a) The food industries may be induced (or obliged by law) to take muslim food rules into consideration in labelling their products. This approach is likely to cover mostly the foods meant to be exported to muslim countries.

(b) Where muslims are living in sufficient numbers, they should start their own food industries and shops. This is being done in some industrial countries but covers the needs of the community only partially.

(c) Muslim associations assisted by scientists should publish lists of brands or marks of foods using permitted items. As stated above, this is being done by the Islamic Food and Nutrition Council of America.

(d) The householders may, as far as possible, use only primary materials to prepare their meals. However, some materials like vegetable cooking oils may have been subjected to unacceptable processing unknown to the householder.

All the foregoing approaches have been used and found to have their limitations. The problem awaits a more radical solution and requires the attention of muslim scholars, food scientists and community leaders working in collaboration.

9. ACKNOWLEDGEMENTS

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The views expressed in this paper are, however, the author's.

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6. Poultry could in certain cases die of cardiac arrest when stunned by this method.
7. According to the Muslim World Gazetteer published by the Islamic World Congress, Karachi, there are 1200 million muslims in the world of whom 400 million (i.e. 1/3rd) are living in non-muslim countries.
8. SAID SALLAM (Cairo) has recently studied the composition of foods in Germany from the Islamic point of view, while working at the Robert von Ostertag Institute, Berlin. The writer is grateful to him for letting him read his draft report.
9. The ridiculous nature and the "reliability" of declarations on food labels may be judged from the fact that packets of pigmeat (hams, bacon) imported by international hotels in some muslim countries have been found to bear the inscription "prepared from animals slaughtered according to muslim rules".
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DISCUSSIONS

The Chairman:

Thank you very much Prof. Abdussalam for warning us not to eat everything we encounter in foreign countries.

And now all the papers which have been presented in this session are open for discussion. I think it is better to go one paper by one paper. So, now, we shall come to the first paper which was presented by Prof. Dr. Atta-ur-Rahman. He gave us a very informative resume about the efforts which can be done with plants' active principles and believe me it is a very tedious job which needs time, efforts and also complicated instrumental aids.

It is very difficult to decide that there is certain plant which can be used for such things because some of the diseases, their etiologies are not yet clear and I think in near future we may bring some solution to these problems.And as we said this morning the research work on medicinal plants is a sort of a chain, beginning with the investigation of the plants, isolation of their active ingredients, pharmacological and toxicological studies and clinical trials to be done on them. It has to begin with the plant and to end with a preparation in your hands to be used by the patients. If this chain is broken anywhere in between then you are getting nothing of these things. In Arab and in Islamic countries, they have thousands of plants being now investigated and thousands of compounds which have been isolated but they are not completely investigated uptill now. So, I think there are now many Islamic Centers all over the world, they are doing their best in carrying out investigations and we hope that future will bring solution to these problems. Now, we would like Prof. Atta-ur-Rahman to add something.

Prof. Atta-ur-Rahman:

This is very important to understand as to why is it that inspite of all the efforts, very little real progress has been made in sciences.

In our countries, in fact, there is minimal effort. We talk about science, we preach about science, but we are really not doing anything about science. If we look at the total amount of the activity in the area of science in the entire muslim world, it is pathetic. I think pathetic is the word. Let me give you some figures; Pakistan spends 72 million US dollars every year in the area of science, Egypt spends abot 67 million US dollars every year in the field of science and as you compare to the countries of similar sizes, perhaps even of smaller sizes in terms of their population, France, for instance, spends 9477 million US dollars in the field of science, U.K. spends 9962 million US dollars every year in the field of science. That means 60 to 70 million US$ that Pakistan or Egypt or other countries like ours spend, the Western countries of a smaller population are spending 9 thousand to 55 thousand million US dollars. The Federal Republic of Germany is spending 16761 million US$. That is one thing.

The second point is, that science can take off only when a certain critical point is reached. It is like a nuclear explosion. You have to have a certain minimal numbers of scientists actively engaged in science before the science can take off. Before that critical margin is reached, the effort is often largely wasted. What is much more worrying indeed, is; the number of students between the age group of 20-24, involved in university education in the Muslim countries. In Pakistan, only 5% of the youth aged between 20-24 are involved in the university education. In Egypt, the figure is 7%. In many Muslim countries it is in these areas starting from 2%

to 7%. As compared to this, it is 55% in Canada, 38% in Sweden, 33% in Denmark, 30% in Germany and so on. This is the number of students, the percentage of students involved, of that age, in university level studies; and, this is overall picture of the university education. If we look at the division between the Science and the Arts, you find that it is still much lower in Science than it is in buisness-oriented subjects. So, we have talked about science but we have not really seriously done anything about science. The effort is nominal. We have to wake up to the needs of this century, because as I said in my lecture, that "Science is the magic wand", which can transform our nations, but for this, to wave this magic wand, you must have the necessary inputs, and those are not there at the moment.

Dr. Hosam Al-Deen:

I have two questions. First of all, I would like to find out from Prof. Atta-ur-Rahman, about the follow-up of the initial findings that were published in "Tetrahydron Letters" on nigellacea which he and others have described as a potent or a possible anticancer drug. The second question is regarding what he mentioned today about an extract from plant Alchi which has shown to have anti-HIV effect and the other one, I do not know, but, you mentioned the extract as anti-cancerous. I do not know whether it is the same extract or different. Please ellaborate on this point.

Prof. Atta-ur-Rahman:

Working in the field of anticancer drugs, has been largely focused on the Catharanthus alkaloids, Vincristine and Vinablastine. These drugs are used in current medicine, for the treatment of acute leukaemia and a number of other cancers, but because there are apparent minute traces in the leaves, there is an international effort to try to synthesize them. The first synthesis was reported by us in 1978 and there are international reports on it. We have in recent years, developed an isolation procedure which gives us much high yields of the Catharanthus alkaloids. The anti-AIDS activity, that we have found is, from a marine animal. It is the species of Zooanthete, in particular marine animal, and the testing was done at the International Cancer Institute about 8–9 months ago. On the basis of the results obtained at Bethesda, we now have an agreement with Hoffman La Roche in New Jersy, who are looking at the potentials of this substance. Although it certainly has anti-AIDS activity, but, I think, it is too early to say whether it will be a drug ultimately, because a lot of experimentations is needed.

On Nigella side, we have carried on with the work and have now about half a dozen of new substances especially the aqueous soluble portions which contain saponins. These are steroidal glycosides as well as, of course, the alkaloids with which we have been working on. There is little biological data that I can present to you at this stage. Although the work is going on, but I cannot make any clear-cut statement about their activities. We certainly have something interesting in the chemistry, but as far as biological details are concerned, we have to wait. The work is going on right now on different aspects but really, I am afraid, I can not say anything on that in this meeting.

The Chairman:

About the *Nigella sativa* saponins or saponin glycosides, they are generally held in the cap of the seeds, after being extracted with alcohol and petroleum ether,they do produce a depressant effect on the heart and cause lowering of the blood pressure. But if *N. sativa* is being taken orally then these glycosides are hydrolysed and it is known that there is a terpene which is called hedraginine and some other triterpenes also. But they are insoluble and they do not show any biological activity.

Any more questions for Prof. Atta-ur-Rahman. If not, then we move on to the second paper presented by Dr. Kadi, on "The use of natural immune enchancers in the treatment of far-advanced cancers". I have some questions for him. I want to ask at first, was there any side-effect encountered? And secondly, I think, uptill

now, you are using the raw seeds. Did you or have you thought of using the *N. sativa* oil itself or the volatile oil or some of the other active ingredients?

Dr. Ahmed El-Kadi:

I start with the second question then the first one.

We elected to use the crude material, the entire *Nigella sativa.* We grind it so it is in powder form, in order to facilitate its absorbtion, but we did not elect to use the extract. Now, this was done on purpose and I know it will sound unscientific, because the way we programme today, now-a-days, we should use the isolated, purified form of ingredients. May be we are trying to promote a different approach which we feel that the entire plant if used in its crude form may have a better effect. We also have to prove this by running some control studies when we use only purified ingredients 1 or 2 or 3 and using the crude material. This will come in the future, Insha Allah. I like to raise the point that when we talk about M.I.P. "Multimodality Immunotherapy program", *N. sativa* is only one of several nutritional supplements and nutrition supplement and nutrition by itself is one of the several modalities. It is quite a comprehensive attack on the immune systems.

As regard to the first question of having any undesirable side effects encountered; so far, we have not. Only one of the volunteers had some indigestion, but it subsided. But some good effect, what he thought was that his hair did not fall that much and another lady had the same thing.

The Chairman:

Anyother question on this paper?

The next paper was presented by our colleague Dr. Al-Mazzar on the "Functional and behavioural teratological studies of a certain herbal formulation in rats". Are there any question on his paper? He has done marvellous piece of work right now which is modern pharmacology which has to go through all these steps and all these procedures to prove or to know that the ingredients have no undesirable effects. No enquiries, or no questions? If not so, then we can move to the next paper by Dr. Sabir about the treatment of asthma. Any Question?

Dr. Sabir, I missed the names of the plants which you have used. What were their extracts which possess good antihistaminic effect and mast cells stabilizing effect and so on? Did you isolate or identify any active principle? Is there any toxicological data? What about its clinical trials?

Dr. M. Sabir:

We have used the crude aqueous extract of the whole formula containing nine plants, the names of which were projected in slide no. 2. Investigtions on the activities of individual plant extract is in progress. We have, thus far, not isolated any active principle. This will be taken up in the second phase of our study. The systematic toxicological investigations are also to start in the next phase. The clinical trial is in progress. The initial studies in patients have shown promising effects.

The Chairman:

Thank you very much. The next paper was on some plants which are used in the treatment of ulcers, presented by Dr.Nazimuddin. I have a question for him. Did you measure the level of prostaglandins in the stomach or not? If you have not done it yet, this is something very important to do.

Any more questions or enquiry from Dr. Nazimuddin? If not, then we come to Prof. Abdussalam. He told us to be suspicious of everything we eat abroad and I think the best thing would be not to eat anything except for some vegetables. I have seen in U.K.; in London and Manchester, in Glasgow and also in Edinburgh, that

there is a big Muslim community, mostly from Pakistan, and they have their own shops for Halal meat and things. I have seen that most of the Muslims buy their things from these shops and I think they have no problem.

Now, we have one question about this paper.

Prof. Atta-ur-Rahman:

If I have understood you, Dr. Abdussalam, correctly, you said that one of the reccommendations of this meeting in Jeddah was, that Muslims living in European countries may use meat, for instance, which has not been slaughtered according to Islamic way. Is that orrect? You mean, they can use meat available at the shops, slaughtered by Christians.

Propf. M. Abdussalam:

Yes, that is correct. The meat prepared by Christians and Jews is permitted to Muslims. This is according to the Quran. In Jeddah meeting, we affirmed it, but they were of the opinion that as a constant process, it is better for people living there permanently or almost permanently to make their own arrangements.

The Chairman:

Is the meat of animals who are killed by electric shocks allowed?

Prof. M.Abdussalam:

Well, that was the question raised there. They rejected the hand shock method, whereby the bolt goes direct into the skull and it comes out and the animal gets unconscious. This is a fatal method. Although the animal is slaughtered while it is still alive, but if not slaughtered it dies. So, they said it is cruel. They also rejected stunning by carbondioxide. This is according to Quran that an animal which is suffocated, is not permitted. So, they thought it is also cruel and is not permitted. But electric stunning which is nonfatal, they said that provided minimum current is used and the animal is still alive at the time of slaughter and that it does not affect the quality of the meat, is accepted. Therefore, they appointed a committee. As mentioned, the committee was more or less convinced that these conditions are satisfied. They only wanted one point to be examined further, that it is not cruel to the animal. Here I might say that the opinion of Jeddah meeting was that even if an animal is slaughtered by a cruel method, but slaughtered properly i.e. it is bled by a Muslim or by an "Ahl-alKitab" then it is permitted yet they objected to the cruelty that was involved and that is why they suggested that normal Islamic method should be prefered.

As regard to your remark that you have seen shops in some places. That is true that where the community is large enough for a shop to be profitable, the shop is there. We have many Turkish shops in an area which is called "Small Istanbul", because of 150,000 Turks living there. But we have to remember that not every body cooks his food at home. Many of the workers have to eat at the canteens in the place of their work and there are many families where the women also work. So they buy prepared or semi-prepared food, and as I mentioned one example of pure vegetable oil having stearate in it which may have come from animal sources,i.e. prohibited animal sources. The difficulty is not completely solved because they cannot import everything from their home country. They cater to taste rather than complete purity in the Islamic sense, which is very difficult.

Prof. Malik Mubashar:

I thought only food prepared by Jews and not by Christians is allowed for Muslims.

Prof. M. Abdussalam:

No, the food prepared by Christians is also allowed. There are 3 "Ahl-alKitab" mentioned in the Holy Quran; the Jews, the Christians and the "Sabaean". The "Sabaean" probably do not exist anymore. They were there at the time of the revelation of those verses. So, the Jews and Christians are "Ahl-alKitab" and their food is permitted for us.

● **الرئيس: الدكتور/ محمد الدخاخني**

في الحقيقة بعض النقاط التي أثيرت من حيث إن الوطن العربي ليس متقدما في مجال النباتات الطبية هذا يخالف الواقع شويه إن الوطن العربي به كثير من الإنجازات وقد بينا ذلك في المحاضرة العامة والتي تمت اليوم الساعة التاسعة صباحا وطبعا لا داعي للتكرار، إنما في الحقيقة القول الذي يقترحه الأخ الـ هو الفيل بتاع الطب النفسي.. يتحدث باللغة الإنجليزية ٥٤٦، تعليقات إلى نهاية الشريط باللغة الإنجليزية...

● **الدكتور / محمد الدخاخني رئيس الجلسة.**

شكرا جزيلا وأرجو أن تكون هاتين الجلستين اللتان عقدتا اليوم قد أثارت شيئا من اهتمام السامعين والموجودين بالنباتات الطبية والفائدة التي قد تنتج منها وكما أرجو دائما عندما نسمع الأبحاث الجديدة نتذكر قول الله سبحانه وتعالى ﴿**وما أوتيتم من العلم إلا قليلا**﴾ فالإنسان مهما يبحث ومهما يتعب نفسه في البحث فإنه في النهاية يجد أنه لا زال على الهامش إلا أننا نأمل ونتطلع إلى مستقبل مشرق وإن شاء الله في السنوات القادمة تكون مراكز أبحاث الطب الإسلامية منتشرة في جميع أنحاء العالم قد أحضرت لنا شيئا جديدا وفسرت لنا بعض النقاط التي لا نفهمها الآن وشكرا لكم وشكرا على اهتمامكم ونتمنى لكل واحد منكم النجاح في عمله وشكرا.

CHAPTER III

SOME SELECTED PAPERS - NOT PRESENTED

1. THE BIO-ACTIVITY OF CERTAIN MEDICINAL PLANTS ON THE STABILIZATION OF RBC MEMBRANE SYSTEM.
   Prof. Dr. J. Sadique, *et al.*
2. EVALUATION OF THE REPRODUCTIVE TOXICITY OF CERTAIN HERBAL FORMULATION IN MICE.
   Prof. Dr. M.M.A. Elmazar, *et al.*

Bulletin of Islamic Medicine, 5: (216-227), 1988.

THE BIO-ACTIVITY OF CERTAIN MEDICINAL PLANTS ON THE STABILIZATION OF RBC MEMBRANE SYSTEM

Professor J. Sadique, Miss Wadha Abdullah Al-Rqobah, Mrs. Mariam F. Bughaith and Dr. Ahmed R. El-Gindy

KUWAIT

INTRODUCTION

Inflammation is a complex phenomenon. It is one of the fundamental responses of cells and tissues to injury caused by noxious and infectious agents. A vast array of substances known as mediators are formed or released either concurrently or successively at the site of injury from various plasma or cell sources in response to an etiological factor[1]. Anti-inflammatory agents exert their effect through a spectrum of different mode of actions[2]. All the steroidal and non-steroidal anti-inflammatory drugs currently available are probably polycompetent in that they are able to modulate more than one mediator or cellular events concerned with inflammatory response[3]. Lysosomes are packed with hydrolytic enzymes. When leucocytes phagocytize an inflammatory agent, they release lysosomal hydrolases which damage the surrounding tissues[4]. Glucocorticoids and several aspirin like drugs have been shown to stabilize lysosomes and this may account for one of their major mechanisms of action[5,6]. It has been reported that since RBC membrane has resemblance to lysosomal membrane, the effect of drugs on stabilization of RBC membrane could be extrapolated to stabilization of lysosomal membrane[7]. The effect of anti-inflammatory drugs including herbal drugs on the stabilization of RBC membrane system subjected to either hypotonic or thermic or their combined stresses have been extensively studied[8-15].

Some of herbal formulae are used successfully in the treatment of human rheumatoid arthritis (RA formula) and allergic rhinitis (AR formula) at Islamic Centre for Medical Sciences, Ministry of Public Health, State of Kuwait. Formula RA and its components *Withania somnifera* roots, *Pyrethrum indicum* roots, *Merendra persica* corm and *Alpinia galanga* rhizome (RA composition: 2: 1: 1: 1 in the above order) were reported to exert anti-inflammatory activity in both acute and chronic inflammation[16]. Similarly AR formula (used for treating allergic rhinitis) having a composition *Cydonia oblangata* seed, *Ziziphus valgaris* fruits and *Cordia latifolia* fruits (3: 5: 6 respectively) was found to be anti-inflammatory and anti-histaminic (unpublished). With a view to understand the mechanism of action of these formulae (RA and AR) and its components, membrane stabilization studies using sheep RBC subjected to a combined hypotonic and heat stresses were undertaken.

EXPERIMENTAL

Preparation of RBC system:

Sheep blood was collected from slaughter house at Kuwait in sterile Alsever's solution (containing 2% dextrose, 0.8% sodium citrate, 0.05% citric acid and 0.42% sodium chloride stored at 4°C). Fresh sheep blood and the blood stored in refrigerator at 4°C for 24-72 hours were used for preparing sheep RBC. Blood was

centrifuged at 2000 rpm for 10 min and then supernatant was discarded. The cells were suspended in isosaline (0.85% NaCl solution) and recentrifuged. After removing the supernatant, 10% cell suspension was prepared using isosaline. In case of unfresh RBC, the cells that responded uniformly in triplicates to heat and osmotic stresses were used.

Preparation of isosaline extracts of the herbal formulae and their components:

Five gm of each of the test materials (RA formula; *Alpinia galanga* - rhizome; *Withania somnifera* - roots; *Pyrethrum indicum* - roots; *Merendra persica* - corm; AR formula; *Cydonia oblongata* - seed; *Ziziphus vulgaris* - fruits and *Cordia latifolia* - fruits) were suspended in 100 ml of 0.85% NaCl solution in conical flasks and kept in the shaking metabolic shaker with a speed of 75 storkes/min for 6 hr. The flasks were kept at room temperature overnight in dark. The extracts were centrifuged in cold and filtered. The clear filtrate was used after adjusting the pH to 7 - 7.4. Similarly standard drugs such as acetyl salicylate (1 mg/ml) and diphenhydramine hydrochloride (1mg/ml) were prepared in isosaline after adjusting the pH to 7 - 7.4.

Effect of various drugs on hypotonic saline and heat induced sheep RBC lysis[8,9,15]:

The incubation mixture consisted of 2 ml hyposaline (0.25%/0.36% NaCl solution), 1 ml 0.15 M phosphate buffer (pH 7.4), different concentrations of drugs made up to 1 ml with isosaline and 0.5 ml 10% sheep RBC suspension. Similarly drug control was put up with isosaline instead of SRBC. They were incubated at 56°C for 30 min, cooled in running tap water and centrifuged at 1500 rpm. The supernatant was measured at 560 nm for haemoglobin release. Control had 1 ml 0.85% saline instead of drug. The control represents 100% lysis. The membrane stabilization activity was calculated as follows:

Percentage membrane stabilization activity =

$$\frac{100\text{-(Drug test value - Drug control value)} \times 100}{\text{control value}}$$

The value represents the average of triplicates ± s.e.m.

In case of studies on LDH leakage from SRBC, the assay system was incubated with different concentrations of RA isosaline extract and acetyl salicylate in presence of hyposoline (0.36% NaCl solution) and 0.1 M phosphate buffer (pH 7.4) at 37°C for 30 min. LDH activity in the supernatant after centrifuging the incubated assay system, was measured using ACA SX Dupont autoanalyser (USA) and haemoglobin was also measured at 560 nm in the supernatant. Control had 1 ml isosaline instead of drug with same composition as described earlier.

RESULTS AND DISCUSSION

Lysosomes are granules containing acid hydrolases which can be released by membrane disruptive agents. The discharge of these hydrolytic enzymes from lysosomes may be responsible for a variety of disorders that effect extracellular connective tissue components. Thus, abnormal fragility of lysosomes and increased extracellular activity of lysosomal enzymes have been implicated in a number of pathological phenomena involving inflammatory processes including human rheumatoid arithritis[17-19].

The ability of anti-inflammatory drugs to stabilize the lysosomal membrane and to inhibit lysosomal enzyme release have been investigated[20-22]. Anti-inflammatory agents such as indomethacin, phenylbutazone and flufenamic acid have been shown to inhibit hydrolase release from liver lysosomes[23,24].

The compounds stabilizing lysosome membrane inhibit the release of enzyme content and occurrence of inflammation[25]. Reinhart[26] has reported the beneficial effect of bioflavonoids in rheumatoid arthritis.

Flavonoids (rutin and tri-hydroxy ethyl rutin) exert stabilizing effect on the lysosomes in vitro[27] and (+) - Cyanidanol - 3(+)- catechin in vivo in rats[28]. Hence anti-inflammatory activity of drugs may be exerted through stabilization of lysosomal membrane.

Many workers have used RBC system to establish the membrane stabilizing activity of drugs[8-15] since RBC membrane resembles lysosomal membrane[7].

Glenn and Bowmann[29] have found that lysis produced by a combination of heat and hypotonicity seems to be more sensitive than produced by either condition alone. Hence in the present study, a combination of heat and osmotic stresses was chosen to produce the lysis of sheep erythrocytes.

When fresh sheep RBC was used in the present investigation, a biphasic response was observed i.e. a particular concentration offered maximal protection against osmotic and heat induced lysis of SRBC and higher concentrations of drugs caused lysis. From Fig. 1, it can be noted that AR extract (used for treating allergic rhinitis) showed a maximal membrane stabilizing activity (59.3%) at a concentration of 12.5 mg in the test system whereas RA extract (used for treating rheumatoid arthritis) gave a maximal response (47.74%) at a concentration of 24.9 mg in the test system. Diphenhydramine hydrochloride, an anti-allergic compound[30] exerted a maximal protection (50%) at a concentration of 500 µg in the test system whereas acetyl salicylate in a similar concentration exhibited weaker membrane stablization activity (8.27%). In these studies, 0.25% hyposaline and 0.15 M phosphate buffer were used[31].

A number of lipid soluble non-steroidal anti-inflammatory drugs prevent hypotonicity induced haemolysis but they share the property with beta adrenolytics[32], local anesthetics[33], tranquilizers[33] and anti-histaminics[34]. Colchicine was also found to stabilize hypotonicity induced lysis of amphibian erythrocyte membrane[35]. The earlier report[36] suggested that the low concentrations (10^{-8} - 10^{-3} M) of the lipid soluble or surface active compounds protect the membrane from osmotic, mechanical or acid lysis but higher concentrations (about 10^{-4} - 10^{-3} M) produce lysis of membrane. It was also reported by several workers that alcoholic fraction of some anti-inflammatory medicinal plants and indomethacin showed a biphasic activity in hypotonicity induced HRBC lysis[10,14,30].

Similarly AR formula is found to have anti-inflammatory and anti-histaminic activity (unpublished). In the present investigation, membrane stabilization activity of RA and AR formulae may suggest the possibility that the anti-inflammatory activity of these formulae may be through the stabilization of lysosomal system. Further, diphenhydramine hydrochloride, an anti-allergic compound, showed a biphasic membrane stabilization activity in the present investigation like anti-histamines[34].

From Fig. 2, it can be noted that AR formula and two of its components *Ziziphus vulgaris* and *Cordia latifolia* showed a biphasic response against heat and hyposaline induced RBC lysis in case of unfresh RBC where same composition of phosphate buffer 0.15 M and hyposaline 0.25% was maintained. It is interesting to observe that similar concentrations of AR extract (about 12.5 mg) showed the highest activity in both cases of fresh and unfresh RBC system. However, the higher percentage of membrane stabilization activity for this concentration was noticed when unfresh erythrocytes were used. *Cydonia oblongata* did not show any membrane stabilizing activity.

It was reported that low concentrations of reserpine, tranquilizers and local anaesthetics reduce the release rate of catecholamines from chromaffin granules but accelerate release rate at higher concentrations[37,38]. The mechanism of stabilization of erythrocyte membrane was attributed to the fact that these compounds increase critical haemolytic volume (Vc) of erythrocyte[39]. This might be due to an actual increase in membrane area or change in membrane viscoelasticity. At sublytic concentrations, these drugs overexpand the membrane and increase the permeability which results in lysis of cells. AR formula has been

found to possess anti-flammatory and anti-histaminic activities (unpublished). The membrane stabilization activity of AR formula may play a role in its anti-inflammatory activity.

The membrane stabilization activity of AR formula may also be involved in its anti-histaminic activity. It is well known that many anti-allergic agents can prevent histamine release from rat mast cells[40]. Ennis *et al*[41] have postulated that prevention of histamine release from sensitized rat mast cells under exposure to specific antigen may be due to the stabilization of membrane of mast cells. Similarly, Akagi *et al*[40] suggested that NCO - 650, a new anti-allergic agent which prevents histamine release induced by compound 48/80 may promote this activity by stabilization of membrane system. So, it is possible that anti-histaminic activity of AR formula may be due to membrane stabilization effect.

From Fig. 3, it can be noted that isosaline extract of RA formula at a concentration of 49.8 mg showed maximal SRBC stabilization activity when unfresh SRBC system was used and the effect was dose dependent. This activity at this concentration was the highest (96.8%) among its components and acetyl salicylate (1 mg). *Pyrethrum indicum* at this concentration showed 93.5% activity and its lowest concentration (12.45 mg) exerted higher activity (79%) than RA formula and its other components at a similar concentration. After reaching 90% activity at a concentration of 24.9 mg, the membrane stabilization activity of *Pyrethrum indicum* did not increase proportionately with further increasing concentrations. The isosaline extract of *Withania somnifera* exhibited a maximal membrane stabilizing activity of 88.9% at a concentration of 49.8 mg. This drug also showed a dose dependent membrane stabilization activity and the activity showed a steep rise in the first two concentrations. There was not much difference between second and third concentrations. *Merendra persica* evoked the highest activity of 86.6% at a concentration of 49.5 mg. There were sharp rises in the first two concentrations followed by slow rises in the last two concentrations. *Alpinia galanga* was similar to *Merendra persica* in the concentration membrane stabilization activity profile but the magnitude was smaller than that of the latter. It showed the highest activity of 73.8% at a concentration of 48.6 mg. Membrane stabilization activity profile for acetyl salicylate was resembling that of *Withania somnifera* with much lesser activity in all the concentrations, the highest activity being 46.9% at a concentration of 1 mg.

It is interesting to note that unfresh SRBC system exhibited the higher membrane stabilization response for RA formula, AR formula and acetyl salicylate compared to fresh SRBC. It is suggested that non-steroidal anti-inflammatory drugs interact with biological membranes, the proteins being main binding sites for these drugs in biological membrane[42] *in vitro.* Hence, in case of unfresh SRBC, there is the possibility of changes in the fluidity of membrane system and so, more accessibility and better binding of RA formula, AR formula and acetyl salicylate with proteins of membranes of unfresh SRBC so that higher activity has been observed. Report on binding of several membrane active drugs to albumin and also on binding of these drugs to erythrocyte membrane using a fluorescent probe, 8-anilino - 1 - naphthalene sulphonate is available[43]. Anti-inflammatory activity of several agents has been tested *in vitro* on the basis of prevention of heat induced albumin denaturation by anti-inflammatory drugs[44-46]. We too have found that aqueous extract of RA formula, its components viz. *Withania somnifera, Alpinia galanga, Pyrethrum indicum, Merendra persica,* AR formula and acetyl salicylate are able to prevent heat induced bovine serum albumin denaturation (unpublished). This observation is in concurrence with the present results on SRBC stabilization against hypotonicity and heat induced membrane lysis by these drugs. A significant role of erythrocyte proteins in the maintenance of structural integrity of erythrocyte membranes has been cited[47]. Hence SRBC membrane stabilizing effects of isosaline preparations of currently tested drugs may be due to the binding of active principles of herbal drugs with proteins of SRBC membranes.

Lactate dehydrogenase (LDH) in erythrocyte is involved in the glycolytic pathway. Its molecular weight is 1,30,000[48] whereas molecular weight of haemoglobin is 68,000[49]. It has been reported that during the stage of haemolysis, there are breaks or holes in membranes as shown by electron microscopy[50]. Conventionally,

haemoglobin has been selected as the marker for studying the leaky nature of RBC membrane system[8]. We were interested in knowing whether LDH, an intra-cellular metabolic enzyme having higher molecular weight than haemoglobin is released by hypotonicity induced RBC lysis and if so, whether RA formula and acetyl salicylate are able to prevent LDH leakage. For this purpose, LDH activity and haemoglobin concentrations were measured simultaneously. From Fig. 4, it can be noted that when unfresh RBC subjected to different hypotonic stresses including distilled water was incubated at 37°C for 30 min, distilled water treatment released maximally LDH and haemoglobin from SRBC followed by 0.36% NaCl solution and other concentrations of NaCl solutions. There was a close similarity between LDH leakage and haemolobin release from SRBC depending upon hypotonicity. Similarly, when unfresh RBC was incubated with different concentrations of isosaline extracts of RA formula and acetyl salicylate in hyposaline medium at 37°C for 30 min, RA extract at a concentration of 49.6 mg prevented maximally LDH leakage (90.9%) and haemoglobin release (83.3%) in comparison to control having no RA extract (Fig. 5). Acetyl salicylate at a concentration of 1 mg prevented LDH leakage (51.5%) and haemoglobin release (41.75%) in comparison to control having no drug (Fig. 5). So, LDH leakage measurements are also sensitive in monitoring the RBC membrane integrity and it has an added advantage that the coloured herbal extracts which will overshadow the haemoglobin colour when measured at 560 nm will have no interference in LDH activity measurements. Interestingly, membrane stabilization values for RA formula and acetyl salicylate at the highest concentration on the basis of haemoglobin measurements (Fig. 3) under experimental condition of hypotonic and heat combined stress which is more sensitive[29] are more closer to LDH leakage prevention values. From all these studies, it can be inferred that RA formula, its components, AR formula, its components except *Cydonia oblongata* and non-steroidal anti-inflammatory drug acetyl salicylate were able to stabilize sheep RBC membrane against osmotic and heat combined stress. Since the effects on RBC membranes can be extrapolated to lysosomal membrane system[7], the anti-inflammatory activity reported for certain herbal recipes viz RA formula, its components[16] and AR formula (unpublished) may be evoked through mechanism of lysosomal membrane stabilization. The components of AR formula except *Cydonia oblongata* may be also able to stabilize lysosomal membrane system.

SUMMARY

Hypotonicity and heat induced sheep erythrocytes lysis was chosen to study the membrane stabilizing activity of RA formula, its components viz. *Withania somnifera, Pyrethrum indicum, Merendra persica* and *Alpinia galanga* and AR formula and its components viz. *Ziziphus vulgaris, Cordia latifolia* and *Cydonia oblongata* and acetyl salicylate and diphenhydramine hydrochloride, an anti-allergic compound. When fresh sheep RBC (SRBC) was used, isosaline extracts of RA formula, AR formula, diphenhydramine hydrochloride and acetyl salicylate showed a biphasic response in membrane stabilization i.e. higher concentrations caused the lysis of membranes. A similar response was seen in case of AR formula and its components when unfresh SRBC was used. Better dose dependent responses were observed for RA formula, its components and acetyl salicylate when unfresh SRBC system was employed. RA formula and acetyl salicylate prevented LDH leakage from SRBC. It has been proposed that these drugs exert anti-inflammatory activity possibly by stabilization of lysosomal membrane system.

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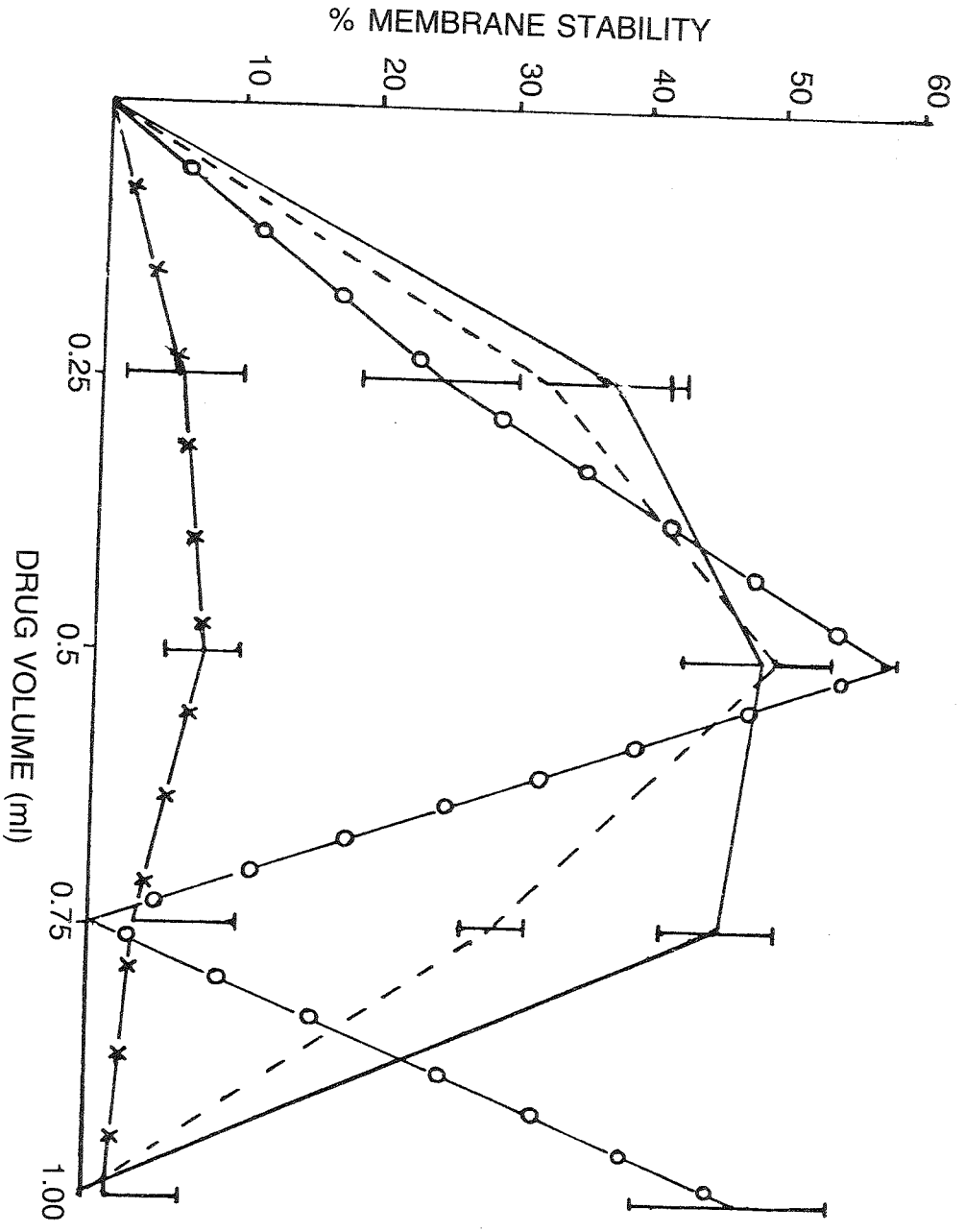

Fig. 1: The effect of isosaline extracts of certain herbal formulae on membrane stabilization in fresh SRBC subjected to hypotonic and heat stresses. 0.25% NaCl and 0.15 M phosphate buffer, pH 7.4 were used.

o——o AR formula (25 mg/ml)
- - - - - RA formula (49.8 mg/ml)

——— Diphenhydramine hydrochloride (1 mg/ml)
X——X Acetyl salicylate (1 mg/ml)

The values represent the mean of triplicates ± s.e.m.

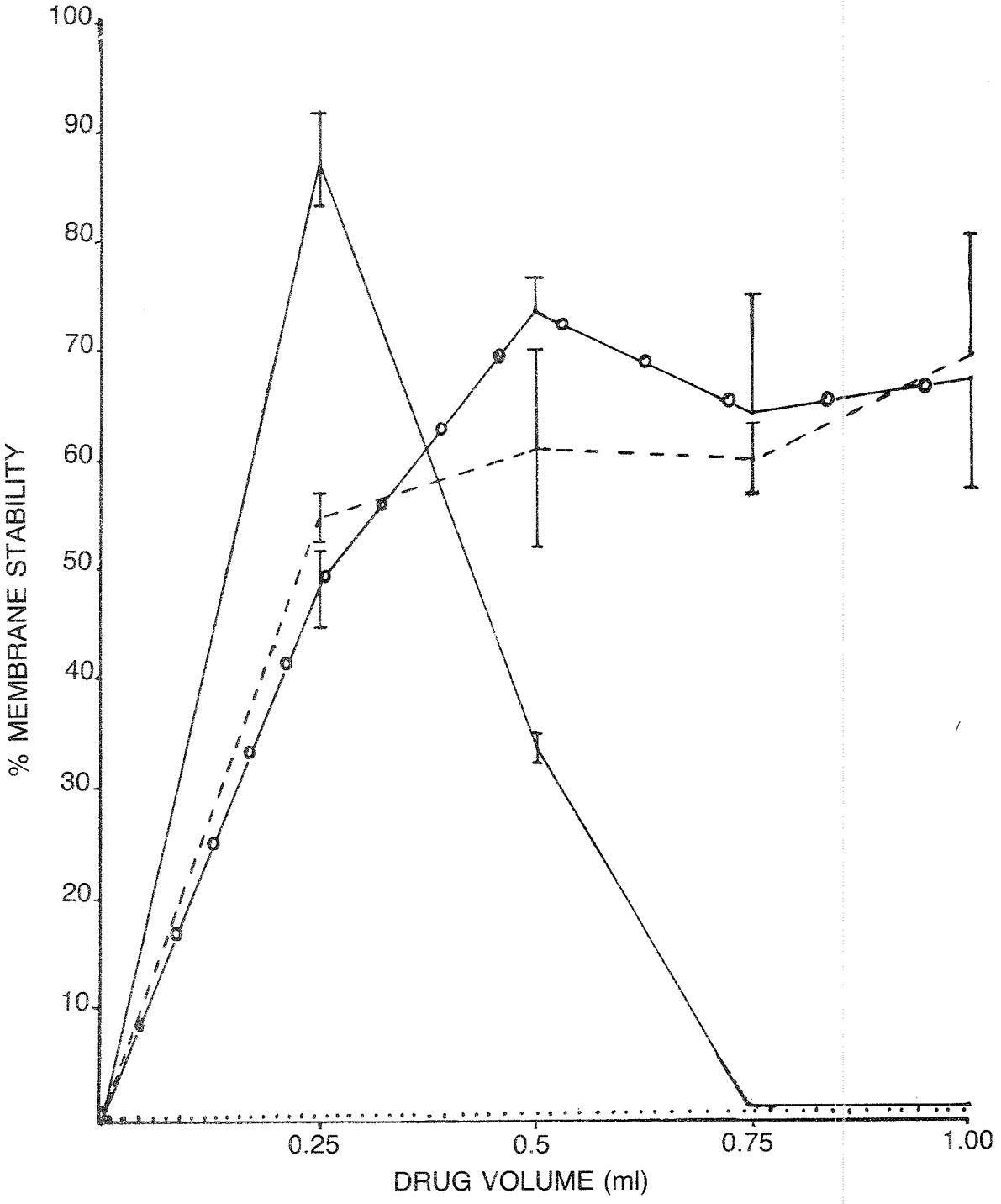

Fig. 2: Membrane stabilizing effect of AR formula and its components on unfresh SRBC subjected to hypotonic and heat stresses. 0.25% NaCl and 0.15 M phosphate buffer, pH 7.4 were used.

——— AR formula (49.8 mg/ml)
o———o *Cordia latifolia* (49.8 mg/ml)
– – – – – *Zizyphus vulgaris* (49.8 mg/ml)
• • • • *Cydonia oblongata* (49.8 mg/ml)
The values represent the mean of triplicates ± s.e.m.

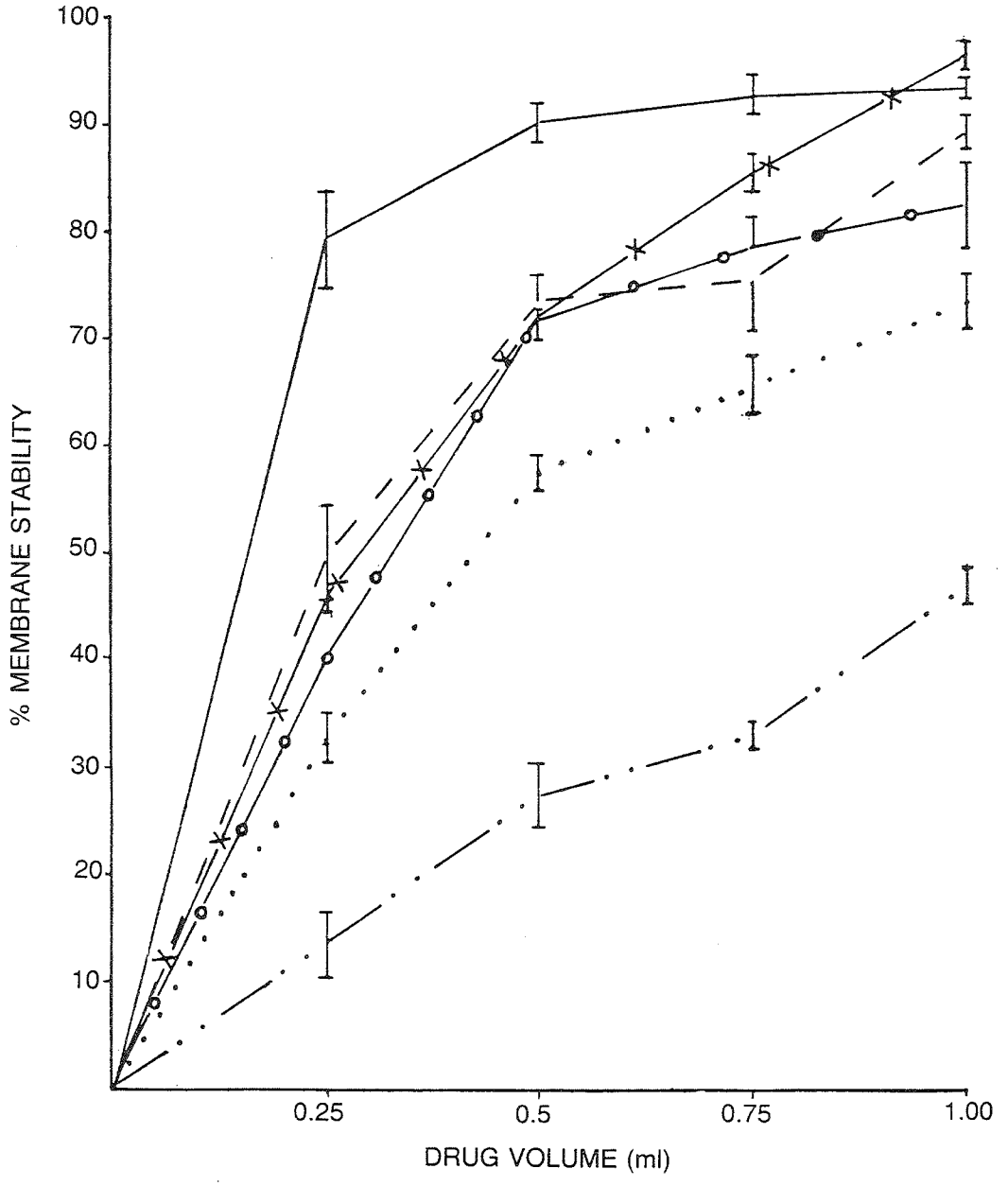

Fig. 3: Membrane stablizing effect of RA formula, its components, and acetyl salicylate on unfresh SRBC subjected to hypotonic and heat stresses. 0.36% NaCl and 0.15 M phosphate buffer, pH 7.4 were used.

X——X RA formula (49.8 mg/ml)
——— *Pyrethrum indicum* (49.8 mg/ml)
– – – – – *Withania somnifera* (49.8 mg/ml)
o———o *Marendra persica* (49.54 mg/ml)
• • • • *Alpinia galanga* (48.64 mg/ml)
• •–• • *Acetyl salicylate* (1 mg/ml)

The values represent the mean of triplicates ± s.e.m.

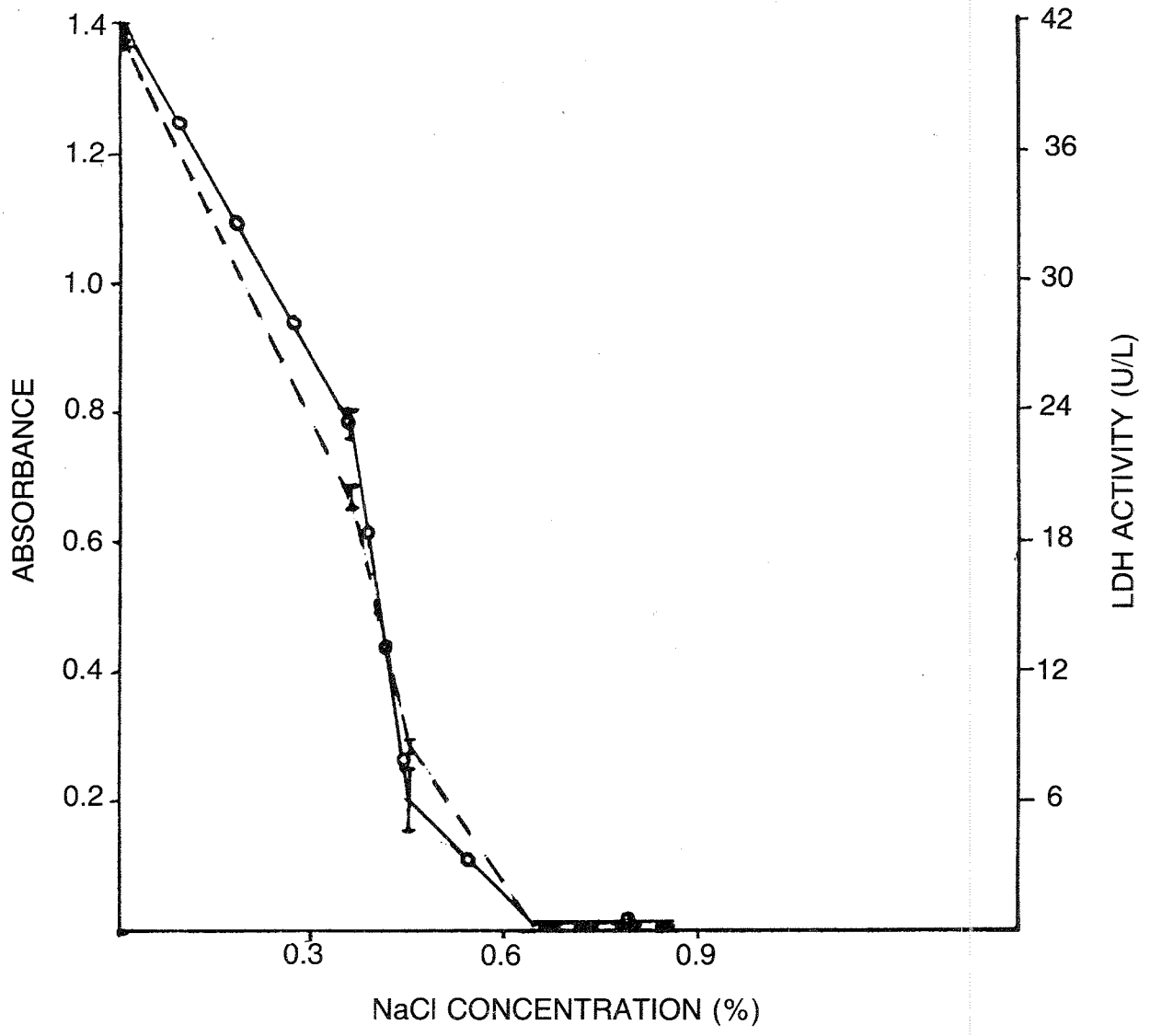

Fig. 4: The effect of different concentrations of NaCl solution on the release of haemoglobin and LDH from unfresh SRBC incubated at 37°C for 30 min.

o——o LDH activity

- - - - - - Haemoglobin absorbance measured at 560 nm.

The values represent the mean of triplicates ± s.e.m.

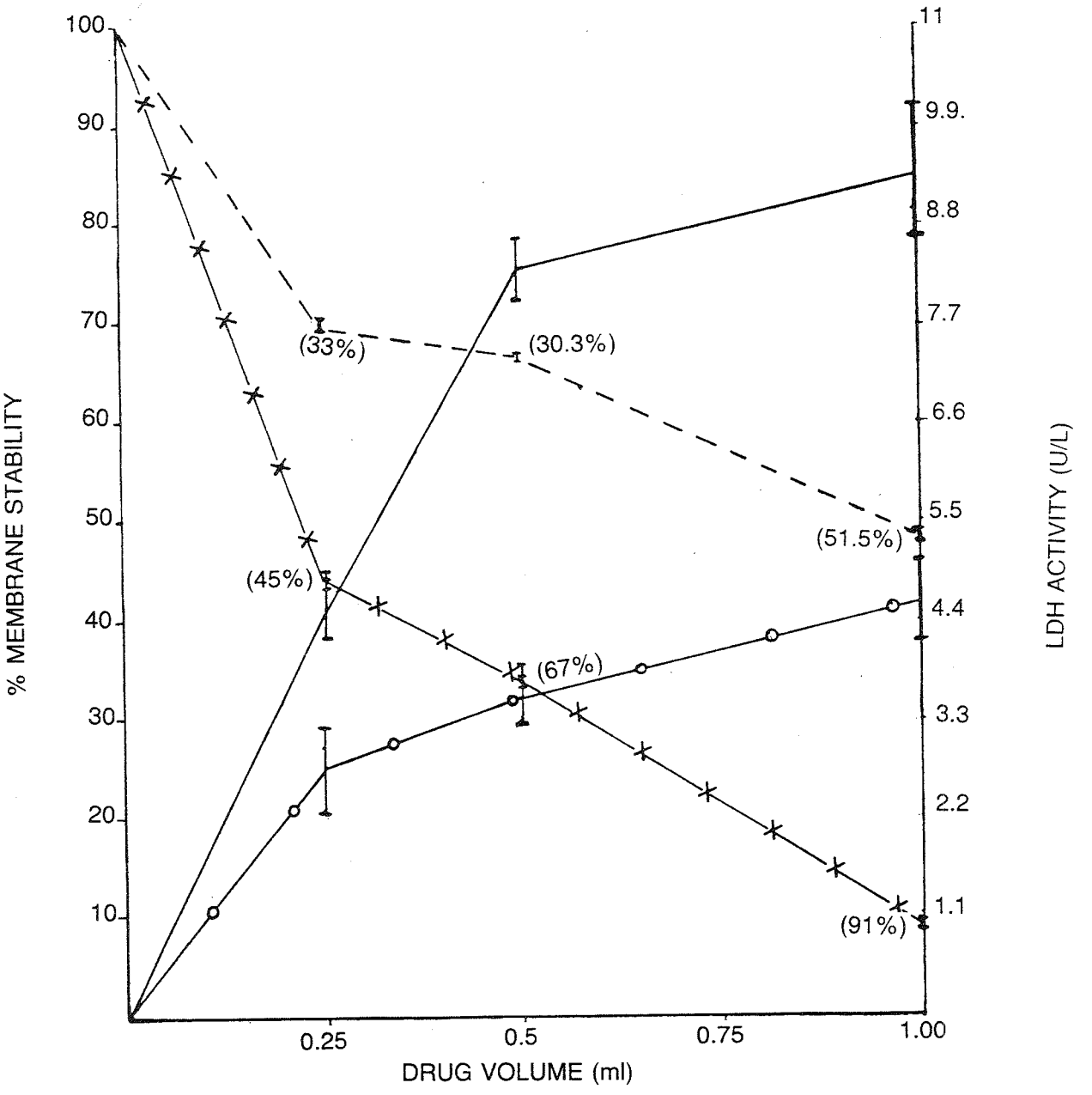

Fig. 5: The effect of RA formula and acetyl salicylate on the release of haemoglobin and LDH from unfresh SRBC subjected to hypotonic stress at 37°C.

——— % membrane stability for RA formula (49.6 mg/ml) on the basis of Hb release

o——o % membrane stability for acetyl salicylate (1 mg/ml) on the basis of Hb release

LDH activity (U/L) released in presence of different concentrations of RA extract.

– – – – LDH activity (U/L) released in presence of different concentrations of acetyl salicylate.

The values in parenthesis indicate percentage prevention of LDH leakage by RA extract and acetyl salicylate.

The value represent the mean of triplicates ± s.e.m.

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EVALUATION OF THE REPRODUCTIVE TOXICITY OF CERTAIN HERBAL FORMULATION IN MICE

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Abstract

Recently, a herbal formulation, consisting of the roots of *Withania somnifera* Linn., *Pyrethrum indicum* D.C., corm of *Merendra persica* Linn. and rhizome of *Alpinia galanga* Wild. (2:1:1:1) has been found, in our laboratories, to exert promising anti-inflammatory activity in animal models.

To assess the teratogenic and mutagenic effects of the formulation, male and female mice were given the aqueous herbal extract, mixed with drinking water (12.5 or 25 mg/ml), for 2 hr. (9-11 a.m.). daily for 6 days before, 5 days during mating and until day 19 of gestation. Thereafter, the females were sacrificed and fetuses examined. The high dose group had significantly lesser degree of late resorptions and male/female ratio. No difference in gross malformation rate was observed compared with matched controls. The fetuses of the low dose group showed retarded caudal ossification, and those of the high dose group had higher frequency of extra ribs. On the other hand the males had extended treatment for upto 50 days and remated, 5 days later, with untreated females (1:3); all females were sacrificed 10 days after mating period and examined for dominant lethal mutations. There was no difference between the groups in the number of males mated or preimplantation embryonic loss. Post-implantation loss due to mating with low dose males was significantly less. Further, the spermatozoa collected from the cauda epididymis of sacrificed males were examined for sperm head abnormalities. There was no significant difference between the groups which may rule out a mutagenic effect of the extract during sperm maturation.

The extract (1g/kg, orally for 5 days) exerted a weak, but significant estrogenic and androgenic activity in overiectomized and castrated adult mice respectively, but not in immature 24-day old mice. The extract did not possess any progestogenic activity.

INTRODUCTION

The medicinal plants *Withania somnifera, Pyrethrum indicum, Merendra persica,* and *Alpinia galanga,* enjoy considerable reputation and have been recommended and used for a variety of diseases in traditional medicine[1-5]. They have been used as anti-rheumatic, anti-inflammatory, aphrodisiac and as a general tonic. *Withania somnifera* is especially used as uterine tonic in leucorrhoea, habitual miscarriage and also in spermatorrhoea and premature ejaculation[6-8]. The combination of these plants has been used effectively in the treatment of clinical arthropathies[9]. The anti-inflammatory activity was evaluated and confirmed experimentally[10], and their combination was pharmaceutically formulated as tablets and being used clinically for the treatment of rheumatoid arthritis in Islamic Centre for Medical Sciences, Ministry of Public Health, Kuwait.

The present study was designed to investigate their possible teratogenic and mutagenic effects in mice, as a part of assessment of their safety.

MATERIALS AND METHODS

Composition of the formulation:

The formulation (R.A.) consists of the powder of dried roots of *Withania somnifera,* Linn. (Solanaceae), rhizome of *Alpinia galanga,* Wild (Zingeberaceae), corm of *Merendra persica,* Linn (Liliaceae), and roots of *Pyrethrum indicum,* D.C. (Asteraceae) in a ratio of 2:1:1:1 parts respectively.

Preparation of the extract:

The extract was prepared by mixing 125 g of powdered RA with 2.5 litre phosphate buffer pH 7.5 (KH_2PO4/Na_2HPO4,1/15 M). The mixture was stirred (250 r.p.m.) using an electrical stirrer (Laboratory Supply Company, West Germany) in a water bath at 37°C for 5 hours. The mixture was then filtered through Whatman No. 1 filter paper, and the filtrate stored in the deep freeze at −20°C, and used within a week. One ml of the filtrate is equivalent to 50 mg of RA extract.

Animals:

Male (35-45 g) and female (25-40 g) Swiss albino mice were used in the present experiment. The animals were maintained on standard pellet diet (86/A; Bugbrooke Mills, Northampton) and water *ad libitum,* unless otherwise stated.

Doses:

In the present experiment, low (L) and high (H) dose levels of RA were given mixed with drinking water or by gavage. These doses were chosen, according to preliminary experiments, to be equivalent to 10 and 20 times, respectively, on mg/kg basis of the maximal allowed clinical doses[9]. The low dose was comparable to the clinical dose based on surface area ratio.

Drug administration:

Three groups of both males and females (10 males and 30 females per group), were selected as control, L and H dose groups. The males were caged individually, while females were caged as 3 animals per cage. Drinking water was removed from all cages at 7-9 a.m. daily. Both males and females were given water, or extract mixed with drinking water (12.5 or 25 mg/ml) for 2 hours (9-11 a.m.) for the control, L and H dose groups respectively.

Fertility and teratogenicity studies:

Administration of extracts was continued daily for 6 days before, and during a mating period of 5 days. The extract consumption was measured daily. Mating of animals was performed by caging 3 females with the same male overnight for 5 consecutive nights or until the animals conceived. In the morning, the females were examined for the presence of vaginal plugs. The day of the presence of a vaginal plug was designated day one of pregnancy. The administration was continued until day 19 of gestation, when the animals were sacrificed by cervical dislocation, and the fetuses removed by caesarian section. The number of live and dead fetuses and resorption sites were counted and the fetuses removed, weighed and examined macroscopically for gross defects. They were then fixed in 70% alcohol and subsequently dissected to examine for visceral defects. All

fetuses were then alizarin stained and the skeletons examined. All uteri with no signs of pregnancy were stained with ammonium sulphide to examine for the presence of implantation sites. In addition, the number of males that mated and of females that became pregnant in each group were also recorded to assess the effect on fertility.

Mutagenicity studies:

A. Dominant lethal mutations:

Males, from the previous experiment, were continuously given the extract for up to 50 days. They were remated, 5 days later, with untreated females, by caging each male with 3 females for 5 days[11]. All females were sacrificed by cervical dislocation 10 days after the end of the mating period. The uterine horns were examined for live and dead fetuses and resorption sites. In addition, the number of males that mated and of females that became pregnant in each group were also recorded.

B. Sperm head abnormalities:

The same males were then sacrificed, within a week, and the two cauda epididymes were excised. Each was placed in one ml saline, finely minced with scissors and left for one minute for the spermatozoa to diffuse out. A drop of the suspension was spread on a slide, air dried, fixed in absolute alcohol, and stained for 15 min. in a 1% aqueous Eosin Y solution. Two slides per mouse were screened blindly by 3 different investigators for sperm head abnormalities[12]. Results are expressed as mean percentage sperms with abnormal heads per group of animals.

Endocrinological studies:

1. Estrogenic activity:

The estrogenic activity of the extract was assessed by measuring uterine weight of overiectomized and immature female mice as well as estrus induction in adult mice[13].

i. Overiectomized adult mice:

Four groups of 5,5,7 and 11 adult female mice, were overiectomized under nembutal anaesthesia (40 mg/kg, i.p. of nembutal sodium, Abbott Laboratories). Five days later, the animals were given phosphate buffer (20 ml/kg, by gavage), estradiol (0.1 µg/mouse, s.c.) and extract (500 and 1000 mg/kg, by gavage) respectively, once daily for 5 days. The animals were killed by cervical dislocation, 24 hours after the last administration. The uterine horns were excised, uterine contents were gently squeezed out; and the wet weight was determined.

ii. Immature mice:

Three groups of 11, 3 and 13, 24-day old female mice were given, phosphate buffer (20 ml/kg, by gavage), estradiol (0.1 µg/mouse, s.c.) and extract (1000 mg/kg, by gavage), respectively, once daily for 5 days. The animals were killed by cervical dislocation, 24 hours after the last administration. The uterine horns were dissected out, their contents were gently squeezed out, and the wet weight was determined. The body weight of the animals was also determined at the beginning and end of the experiment.

iii. Induction of estrus in adult mice:

Two groups each of 9 adult female mice, were used. Vaginal smears were taken from each animal twice

daily for 5 days before and during a treatment period of 5 days. Phosphate buffer (20 ml/kg) and extract (1000 mg/kg) were given by gavage once daily, respectively. The number of animals with positive estrus smear was recorded.

2. Progestogenic activity:

The progestogenic activity of the extract was evaluated by measuring the ability to maintain pregnancy in overiectomized mice[14]. Two groups of 7 and 9 pregnant mice were given water or 25 mg/ml extract in the drinking water respectively from day 8-19 of pregnancy. On day 10 of gestation, the animals in both groups, were overiectomized under nembutal anaesthesia (40 mg/kg, i.p). Four pregnant mice were Sham operated at day 10 of gestation and used as a control non-overiectomized group. At day 19 of gestation, the animals were killed by cervical dislocation, and the uterus was examined for the presence of live fetuses, resorptions and implantation sites.

3. Androgenic activity:

The androgenic activity of the extract was investiged by weighing prostate and seminal vesicles of castrated and immature male mice[14].

i. Castrated adult mice:

Two groups of 6 and 5 adult male mice were castrated under nembutal anesthesia (40 mg/kg, i.p). Five days later, the extract was given by gavage at a dose of 1000 mg/kg., once daily for 5 days to the first group. The other group was given 20 ml/kg phosphate buffer. Twenty four hours after the last administration, the mice were sacrificed by cervical dislocation, and the ventral prostate and seminal vesicles were dissected out. The wet weight was determined and compared with that of non-castrated adult males.

ii. Immature mice:

Two groups of 12 and 11, 24-day old male mice were given phosphate buffer (20 ml/kg) and the extract (1000 mg/kg) orally by gavage once daily for 5 days respectively. Twenty four hours after the last administration, the animals were killed by cervical dislocation, and the ventral prostate and seminal vesicles were dissected out and the wet weight was determined. The body weight of the animals was also determined at the beginning and end of the experiment.

Statistical methods:

The results were analyzed using Student's 't' test, Chi-square test or Wilcoxon rank sum test, where appropriate.

RESULTS

Body weight gain and extract consumption:

Body weight of male and female mice as well as their consumption of the extract during treatment period is shown in Figure 1. The extract was given in the drinking water for 2 hours daily in two concentrations (12.5 and 25.0 mg/ml) for both males and females. The animals gradually consumed an increased amount of the extract during the first week of experiment, and reached virtually a constant volume by the end of the second week. The average extract consumed by males was 247 ± 22.9 – 729 ± 101.9 and 600 ± 63.6 – 1777 ± 225.0, and by females was 141 ± 29.8 – 342 ± 35.0 and 303 ± 70.5 – 808 ± 60.3 mg/kg daily for L and H dose groups

respectively. The body weight gain of the males and females in both treated groups was similar to that of the control groups during the treatment period. Female mice in all groups progressively increased in body weight towards the end of gestation period with a concomitant decrease in the dose taken as mg/kg. The volume taken daily was, however, not changed.

Fertility and teratogenicity studies:

The results are shown in Table 1. Two males in each of control and L dose groups failed to mate with any of the 3 females caged with them during 5 successive nights. Therefore, 6 females from each of these two groups were excluded, beside another one pregnant female from H group, escaped from the cage and died. From the remaining animals, 2 females from each of control and H group did not mate successfully and another one control animal which showed positive vaginal plug but was found non-pregnant. There was no significant difference between the groups in the number of males that mated or of females that became pregnant at the end of 5 days mating period. Furthermore, there was no significant differences in the number of live fetuses or advanced resorptions/litter. Delayed resorption rates were significantly lower in H group. A dose related decrease in the male/female ratio was observed and was significant at the high dose level ($P < 0.02$). The gross external malformations, were two runted fetuses from two litters, one fetus with hydrocephallus and one fetus with subcutaneous haemorrhage, in the control group; four runted fetuses from two litters, one fetus with full length cleft palate and one fetus with subcutaneous haemorrhage in the low dose group; three runted fetuses from different litters in the high dose group. There was no significant difference in fetal body weight between the groups.

Skeletal examinations:

The results are shown in Table 2. The fetuses in the L group had retarded caudal ossification, and those of H group had higher frequency of extra ribs. There was no difference between the groups in the degree of ossification or frequency of abnormal fusions of sternebrae.

Mutagenicity study:

A. Dominant lethal mutations:

The results are shown in Table 3. The same two males in the low dose group which failed to mate in the teratology experiment, failed to mate again at the end of the treatment period. The two control males which did not mate earlier, however, succeeded to mate with 1 and 3 females respectively. Another control male died during the experiment. There was no significant difference between the groups in the number of males mated or total number of implants as a measure for (pre-implantation loss). Post-implantation loss (mutagenic index), due to mating with low dose males, however, was significantly less than that of the control group ($P < 0.03$).

B. Sperm head abnormalities:

The results are shown in Table 3. When the males were killed and the sperms were examined for head abnormalities, it was found that, the two males in the low dose group, which failed to mate both at the beginning and end of the experiment, had oligospermia with very high rate of sperms with abnormal heads (63 and 80%) compared with an average of about 4% in the other animals. Their values, therefore, were execluded from the calculation of the mean of the group. In all animals, however, there was no significant difference between the groups in the rate of sperm abnormalities using the Wilcoxon rank sum test.

Endocrinological studies:

1. Estrogenic activity:

The effect of oral extract administration for 5 days on the uterine weight of overiectomized and immature female mice is shown in Figure 2. Administration of 0.1 μg/ mouse estradiol s.c. once daily for 5 days produced a marked increase in the wet uterine weight of both overiectomized (from 31.4 ± 3.2 to 251 ± 24.0) and immature (from 17.0 ± 1.0 to 54.4 ± 6.7 mg) mice. In overiectomized adult mice, the extract produced an increase of 22 and 90% in uterine wet weight, when given in doses of 500 and 1000 mg/kg orally respectively. The effect of the high dose was significant ($P < 0.02$). In immature 24 day old female mice, however, 1000 mg/kg extract had no effect on uterine or body weight.

The effect of oral extract administration on estrus induction in adult mice is shown in Figure 3. Figure 3a shows results extracted from Table 1, where the cumulative % of pregnant mice were recorded during the 5 days mating period. In the third day of mating, 72.7, 83.3 and 92.5% of the control, low and high dose levels of the extract respectively, became pregnant. The results, though dose related are not significantly different, and the effect of the higher dose reached a probability of 0.062. Figure 3b shows per cent of adult non-pregnant mice with positive estrus in a vaginal smear, 5 days before and during treatment with 1000 mg/kg extract orally. Treatment caused a significant increase ($P < 0.03$) of animals with positive estrus during treatment period than before treatment. Administration of phosphate buffer, however, did not produce any significant change.

2. Progestogenic activity:

In all animals, live implants were seen in both utrine horns during overiectomy at day 10 of gestation. Sham operated group (4 animals), maintained pregnancy and had a total of 39 live fetuses (range 8-11) and one resorption in each litter at day 19 of gestation. In overiectomized non-treated group (7 animals), no live fetuses were found, 2 animals had 8 and 9 resorptions and 5 animals had 52 implantation sites (range 8-13). In overiectomized extract treated group (9 animals), no live fetuses were found, all animals had 71 resorptions (range 1-12), and 7 animals had also 28 implantation sites (range 3-11).

3. Androgenic activity:

The effect of 1000 mg/kg RA extract orally for 5 days on prostate and seminal vesicles weight of castrated and immature male mice is shown in Figure 4.

In castrated adult male mice, administration of 1000 mg/kg extract for 5 days caused an increase in the weight of prostate and seminal vesicle by 31.3% (from 65.1 ± 3.3 to 85.5 ± 6.3 mg, $P < 0.02$). Non-castrated adult male mice had prostate and seminal vesicle weight of 185.6 ± 6.3 mg (4 animals).

In immature 24-day old mice, however, there was no significant change in the weight of prostate and seminal vesicle (from 22.6 ± 3.2 to 26.7 ± 3.2 mg). There was also no effect on body weight gain of these animals.

DISCUSSION

The maximal dose of the herbal preparation (RA) recommended for treatment of clinical arthropathies is 4 g/patient daily[9], which is about 57 mg/kg. This dose is equivalent to 520 mg/kg for mice based on surface area ratio, i.e. about 10 times the clinical dose as mg/kg. In the present experiment, the extract was given to mice mixed with drinking water (in two concentrations, 12.5 and 25 mg/ml), for 2 hr. daily during the whole treatment period. The maximal extract consumed by males was 929 and 1777 mg/kg, and by females was 342 and 808 mg/kg for low (L) and high (H) dose groups respectively. Therefore, male mice were exposed to a maximal

concentrations of the extract of 13 and 31 and females to 6 and 14 times that of the human dose (mg/kg) for L and H groups respectively.

The extract in the doses given did not show any signs of toxicity on male and female mice nor affected their body weight gain during treatment period.

Fertility and teratogenicity studies:

Administration of the extract to males and females started 6 days before mating. This covered one estrus cycle in the females and will also detect effects on mature sperms due to exposure of the males to the extract. Further, this design may also detect changes in sexual behaviour, such as changes in libido or potency. These changes are most likely to occur with agents that interfere with hormone secretion or have a central or a peripheral action on the nervous system[15]. This would be reflected as changes in the number of both males and females that successfully mated. In the present experiment, there was no significant difference between the groups in the number of males mated or of females became pregnant at the end of 5 days mating period. At the third day of mating, however, there was a dose-related higher number of females that became pregnant being 72.7, 83.3, and 92.5% for control, L and H groups respectively. These slight differences may suggest some hormonal changes in the animals as a result of extract exposure, particularly its major component, *Withania somnifera*. *Withania somnifera* has been reported to contain the steroidal lactones, Withanolides[16], and has a reputation in traditional medicine in the treatment of reproductive disorders[6-8]. The extract produced a dose-related reduction in delayed resorptions and male/female ratio. The effect of the high dose was statistically significant ($P < 0.02$). Similarly a decrease in male/female ratio was found in the offspring born to rats given the extract 15 days before mating and through gestation period[17]. The results of both experiments (in mice and rats) may indicate that the change in offspring sex-ratio is a result of effects on the females. Males in the rat experiement were not treated. The change in sex-proportion could be due to variation in vaginal and intracervical pH as a result of direct actions of the extract or through a harmone-mediated effect. Changes in pH level affect the motility of spermatozoa containing X and Y chromosomes[18]. In man, male zygotes are formed earlier in the cycle than female zygotes[18,19], and this is related to maternal hormone levels[20]. The finding in the present experiment that the extract induced estrus in mature female mice, could mean that at the time of mating, the treated animals were already late in the cycle which favours fertilization of female zygotes.

There was no significant difference between the groups in fetal weight or frequency of gross malformations. Delayed caudal ossification in the L group and high frequency of extra ribs in the H group, were observed. The delayed ossification was not dose-related, and could reflect the slight, non-significant, decrease in fetal weight in the same group. Therefore, it is not normally regarded as specific embryotoxic effect[15]. The absence of other congenital abnormalities and anomalies in the treated groups, may regard the finding of extra ribs of no toxicological significance[15].

Mutagenicity studies:

Mutagenicity tests are now widely accepted by regulatory agencies as being of some value for prediction of carcinogenic potential. Damage to DNA in germ cells may lead to genetically altered gametes, resulting in early abortions, fetal deaths, stillbirths, or abnormally developed offspring[21]. Chemicals causing chromosomal damage (breaks, re-arrangement, single gene mutation, etc.) are more likely to affect males than females when exposure occures during adulthood. In males, the production of sperm in adult life is continuous and repeated cell divisions during the sperm cycle maximize the opportunities for chemical attack on the chromosomes[15]. The whole process of spermatogenesis takes from about 8 weeks in mice to 10 weeks in rats and man[15]. Chemicals can affect any one or several stages of spermatogenesis and the effect observed depends on the stages affected.

The dominant lethal mutation test in male mice can demonstrate the response of different stages of development of male germ cells to the suspected drug. A dominant lethal mutation is a genetic change that results in the death of the conceptes that inherit it[22]. The main type of genetic damage it detects is chromosomal breakage with a consequent increase in non-viable embryos[22,23]. The test can also detect changes in male fertility. Administration of the extract, in the present experiment, covered the whole period of spermatogenesis in mice, and the results, showed no effect of the extract on fertility of the males or on pre-implantation embryonic loss. Post implantation embryonic loss (mutagenic index), due to mating with L dose males, however, was significantly low.

The sperm-head abnormality assay is an in-vivo technique for the identification of agents capable of causing an increase in the incidence of sperms with morphologically abnormal head shapes in mice[12]. Insults to the spermatogonia or early spermatocytes can lead to a disruption of normal differentiation of the morphology of sperm cells. The shape of sperms is polygenically determined and has a high heritability[12]. About 90% of the agents which induce sperm abnormalities in mice are carcinogens or mutagens, and the interference with the mechanism controlling sperm shape in exposed males may be associated with the induction of transmissible mutations in mice. The results, of the present experiment, showed no treatment related change in the rate of sperm head abnormalities. It is interesting to find that the two males in the low dose group, which failed to mate both at the beginning (teratology experiment) and end (dominant lethal mutation) of the experiment had oligospermia with very high rate of sperms with abnormal heads. This finding may indicate that the test can detect changes in fertility of male mice.

Endocrinological studies:

It was found, in the present experiment, that extract administration increased the cumulative pregnancy rate during the mating period, and altered the sex-proportion of their offspring. Both effects were dose-related and could be hormone-mediated, as discussed previously. Therefore, experiments were designed to investigate that possibility.

It was found that extract administration increased uterine weight of adult (overiectomized), but not of immature female mice. It also induced estrus in adult female mice. These results may indicate that the extract had a slight but significant estrogen-like activity in adult female mice. The effect could be due to direct effect on the uterus or through stimulation of synthesis of gonadal steroids from the adrenals. The adrenals have the biochemical capacity to produce appreciable amounts of gonadal steroids (estrogens, androgens and progestogens)[24]. Liver and fatty tissues can also produce small quantities of estrogens from circulating androgens of adrenal or ovarian origin[25]. The lack of an effect of the extract on uterine weight of immature mice could be related to lower sensitivity of immature uterus to the action of estrogens. In the present experiment an injection of estradiol (0.1 µg/animal, s.c.) produced 7 fold increase in uterine weight of overiectomized adult mice, compared with only 2.2 fold increase in immature mice. The extract produced slightly less than one fold increase in uterine weight of overiectomized adult mice.

The extract did not show any progestogenic activity since it failed to maintain pregnancy in overiectomized mice, in the present experiment, and to prevent estrogen (1 µg/mouse)-induced reduction in the number of embryos implanted, when given to mice during pre-implantation period (unpublished observation), according to the method described by Gidley-Baird *et al* [26].

On the other hand, administration of the extract increased the weight of prostate and seminal vesicle of adult (castrated) by 31%, but not of immature male mice. It also significantly increased the weight of prostate and seminal vesicle of non-castrated adult mice by 30%, with a non-significant increase (from 0.903-1.112 ng/ml, 23%) of plasma testosterone level measured using radio-immunoassay (unpublished observation). The

testosterone level of castrated mice was undetectable, and the estrogen level (measured by radio-immunoassay) of overiectomized and intact mice was not changed by extract administration (unpublished observation). These findings indicate that the extract may increase the synthesis of gonadal steroids (possibly androgens) in the adrenals of both males and females. In females, body fat is an important site for the aromatization to estrogen of circulating androgens of adrenal and ovarian origin[25]. The suggestion of adrenal involvement may be supported by the preliminary finding, that extract administration for 4 months increased the adrenal weight of male and female rats (unpublished observation). The extract could enhance steroid synthesis through an increase of steroidal precursors. Steroidal lactones (Withanolides) of *Withania somnifera,* could be one factor; or the increase in serum cholesterol level due to extract administration[17], could be another factor. It was shown that adrenal steroids are derived from plasma cholesterol[27]. Further work is in progress to investigate these possibilities.

In conclusion, the extract did not exhibit major signs of reproductive toxicity, teratogenicity and mutagenicity in mice. It exerted a weak, but significant estrogen and androgen-like activities in female and male mice respectively. Experiments are in progress, on other species to further assess its safety for use during pregnancy.

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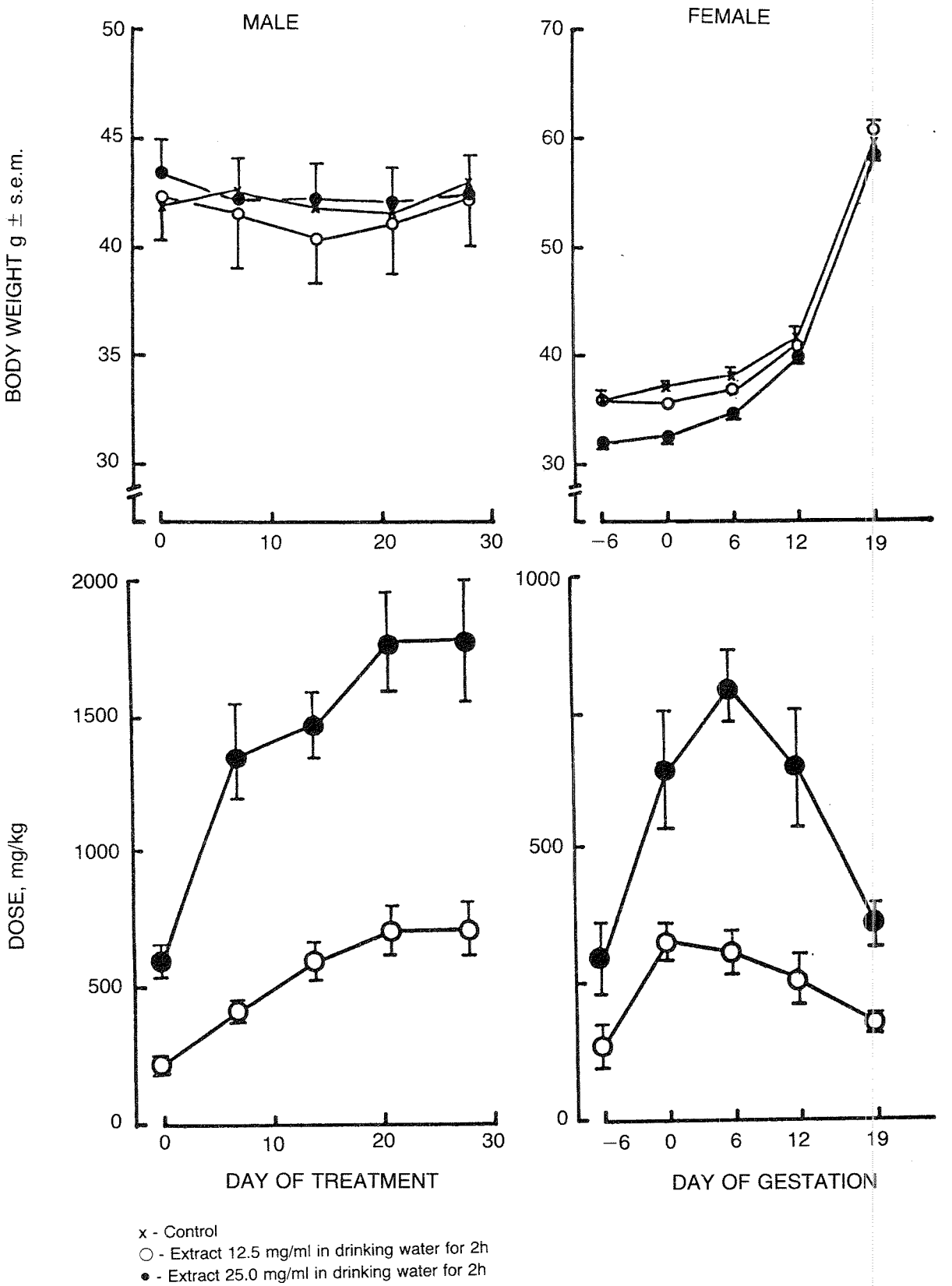

Fig. 1: Body weight and extract consumption of male and female mice during treatment period.

TABLE 1: TERATOGENIC EFFECTS OF THE EXTRACT GIVEN IN THE DRINKING WATER 6 DAYS BEFORE MATING AND THROUGH GESTATION UNTIL DAY 19 OF PREGNANCY

Parameters	Control	Extract 12.5 mg/ml	Extract 25 mg/ml
No. of males mated/Total No.	8/10	8/10	10/10
No. of females with plugs/Total No.	22/24	24/24	27/29
Total No. of implants/No. of litters	244/21	294/24	324/27
$\bar{X}$ ± s.e.m.	11.6 ± 0.47	12.3 ± 0.5	12.0 ± 0.54
Live fetuses/No. of litters	213/21	260/24	299/27
$\bar{X}$ ± s.e.m.	10.1 ± 0.56	10.8 ± 0.5	11.1 ± 0.63
Advanced resorptions/No. of litters	17/10	22/14	23/11
(%)	(6.97)	(7.48)	(7.1)
Delayed resorptions/No. of litters	14/9	12/11	2/2
(%)	(5.74)	(4.08)	(0.62)*
No. of females (%)	90 (42.1)	128 (49.2)	160 (53.5)*
No. of males (%)	124 (57.9)	132 (50.8)	139 (46.5)*
Dislocated hind limbs (%)	16 (7.5)	23 (8.9)	32 (10.7)
Mean fetal weight g ± s.e.m.	1.49 ± 0.06	1.40 ± 0.04	1.48 ± 0.05
Other malformations	2/2 runt	4/2 runt	3/3 runt
	1 Haem.	1 Haem.	—
	1 Hydrocephallus	1 F.L.C.P.	—

⋆: $P < 0.02$ compared with the control group using Chi-square test.

TABLE 2: SKELETAL ANOMALIES IN FETUSES EXPOSED TO THE EXTRACT DURING PREGNANCY

Treatment	No. examined	Retarded ossification		Skeletal variants	
		Sterebral (%)	Caudal[a] (%)	Extra ribs (%)	Malformed Sternebrae (%)
Control	214	33 (15.4)	60 (28.0)	4 (1.9)	37 (17.3)
RA (Low dose 12.5 mg/kg)	260	51 (19.6)	102 (39.2)⋆⋆	10 (3.9)	61 (23.5)
RA (High dose 25.0 mg/kg)	299	45 (15.1)	94 (31.4)	16 (5.4)⋆	67 (22.4)

a: No. of fetuses with less than 8 ossified caudal vertebrae

Results compared with that of the control group using Chi-square test ⋆: $P < 0.05$ ⋆⋆: $P < 0.01$

TABLE 3: EFFECTS OF THE EXTRACT GIVEN IN THE DRINKING WATER FOR 50 DAYS TO MALE MICE, ON DOMINANT LETHAL MUTATIONS (WHEN MATED TO NORMAL FEMALES, 5 DAYS LATER); AND ON SPERM HEAD ABNORMALITIES

Parameters	Control	Extract 12.5 mg/ml	Extract 25 mg/ml
Dominant lethal mutations:			
No. of males mated/Total No.	9/9	8/10	10/10
No. of females pregnant/Total No.	21/27	18/30	22/30
Total No. of Implants	226	216	256
$\bar{X} \pm$ s.e.m.	10.8 ± 0.76	12.0 ± 0.39	11.6 ± 0.44
Live fetuses (%)	200 (80.5)	208 (96.3)	236 (92.2)
$\bar{X} \pm$ s.e.m.	9.5 ± 0.78	11.6 ± 0.43*	10.7 ± 0.49
Resorptions (%)	26 (11.5)	8 (3.7)	20 (7.8)
Sperm Head Abnormalities:			
Sperms with abnormal head mean % ± s.e.m. (No.)	4.43 ± 0.29 (9)	4.33 ± 0.74 (8)	4.9 ± 0.58 (10)

*: $P < 0.03$ compared with the control group using Student's t test.

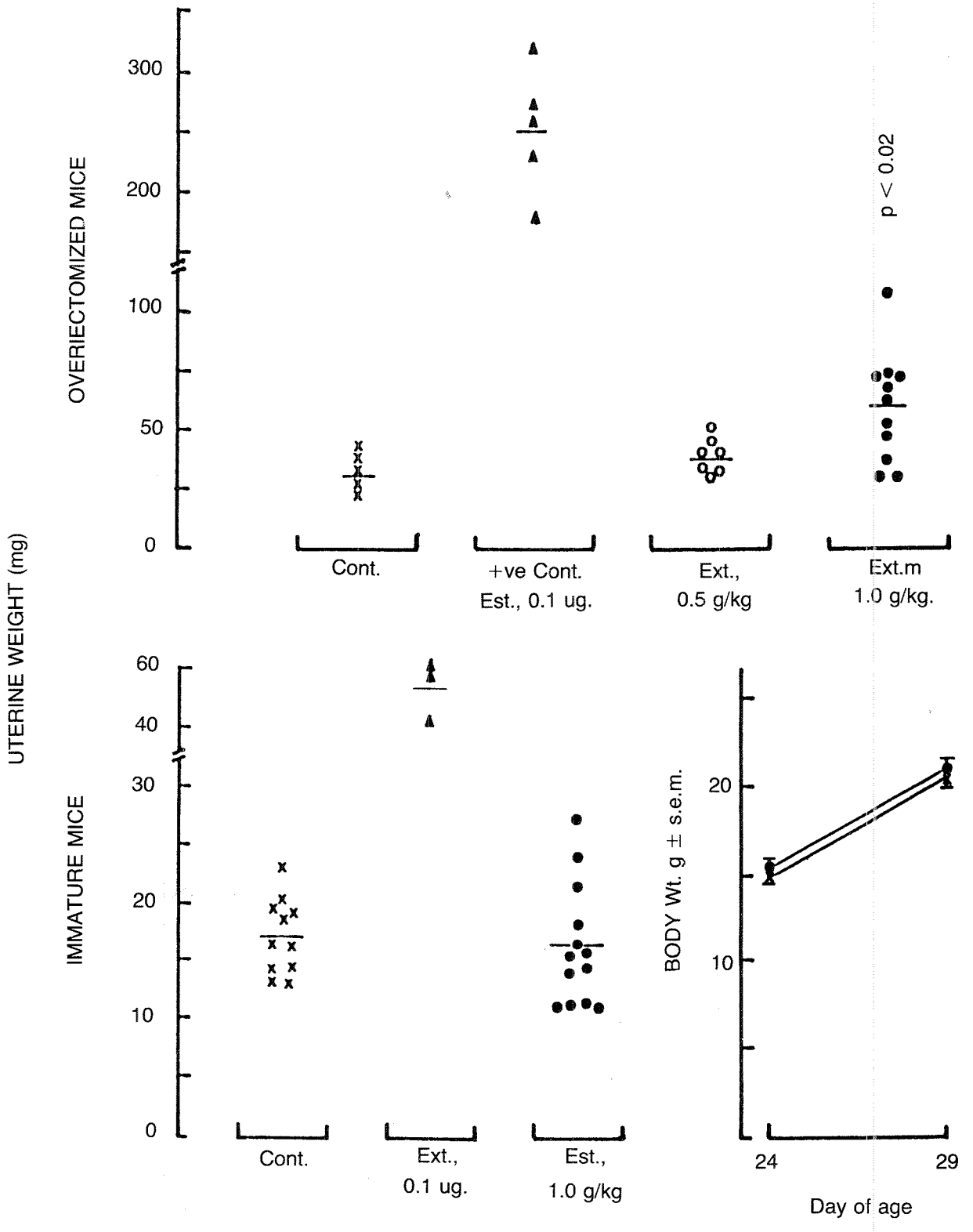

Fig. 2: Effect of extract administration (1 g/kg, orally for 5 days) on uterine weight of mature overiectomized mice, and on uterine and body weight of immature (24 days old) mice.

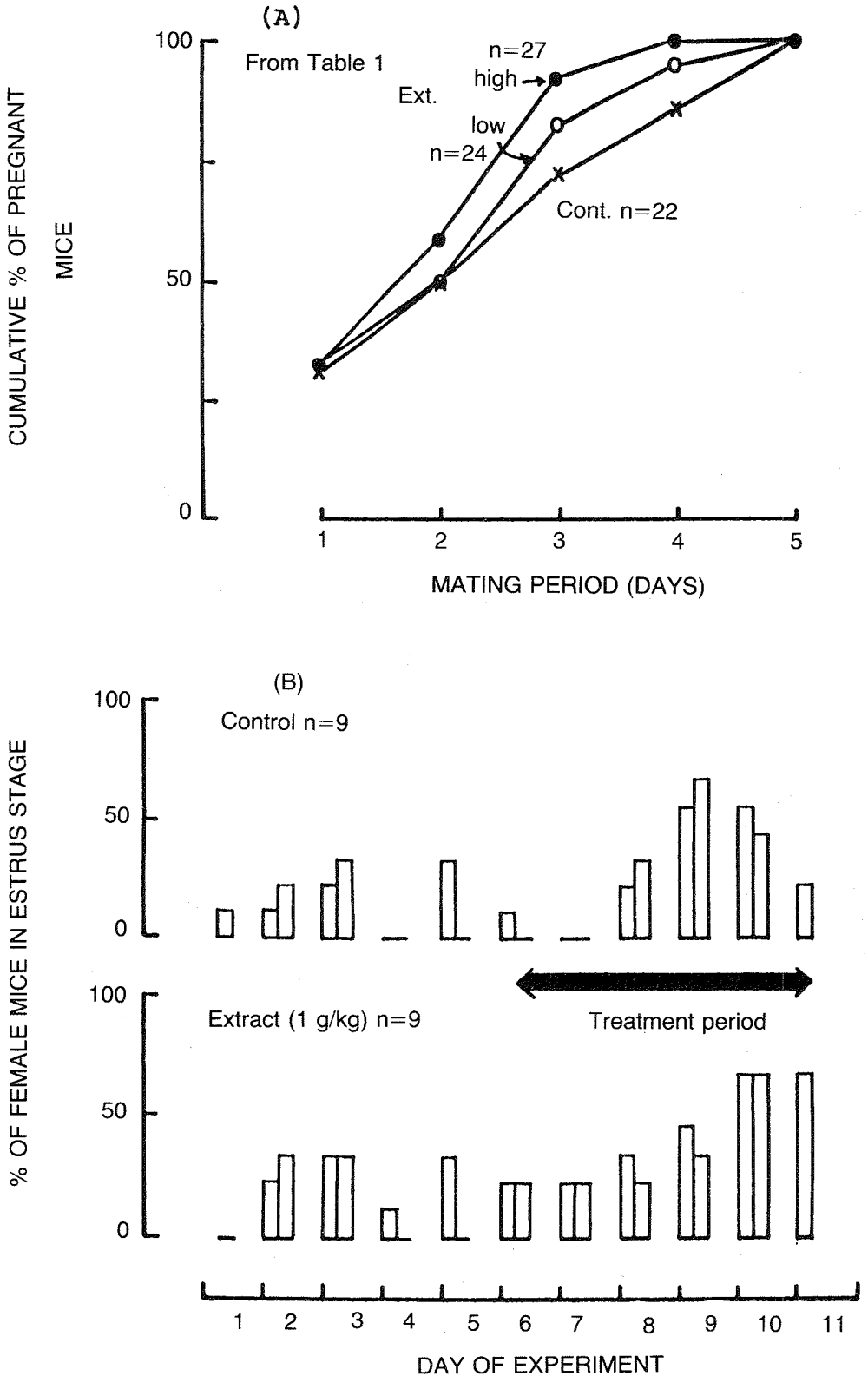

Fig. 3: Effect of extract administration on pregnancy rate (A), and on induction of estrus (B) in mature mice.

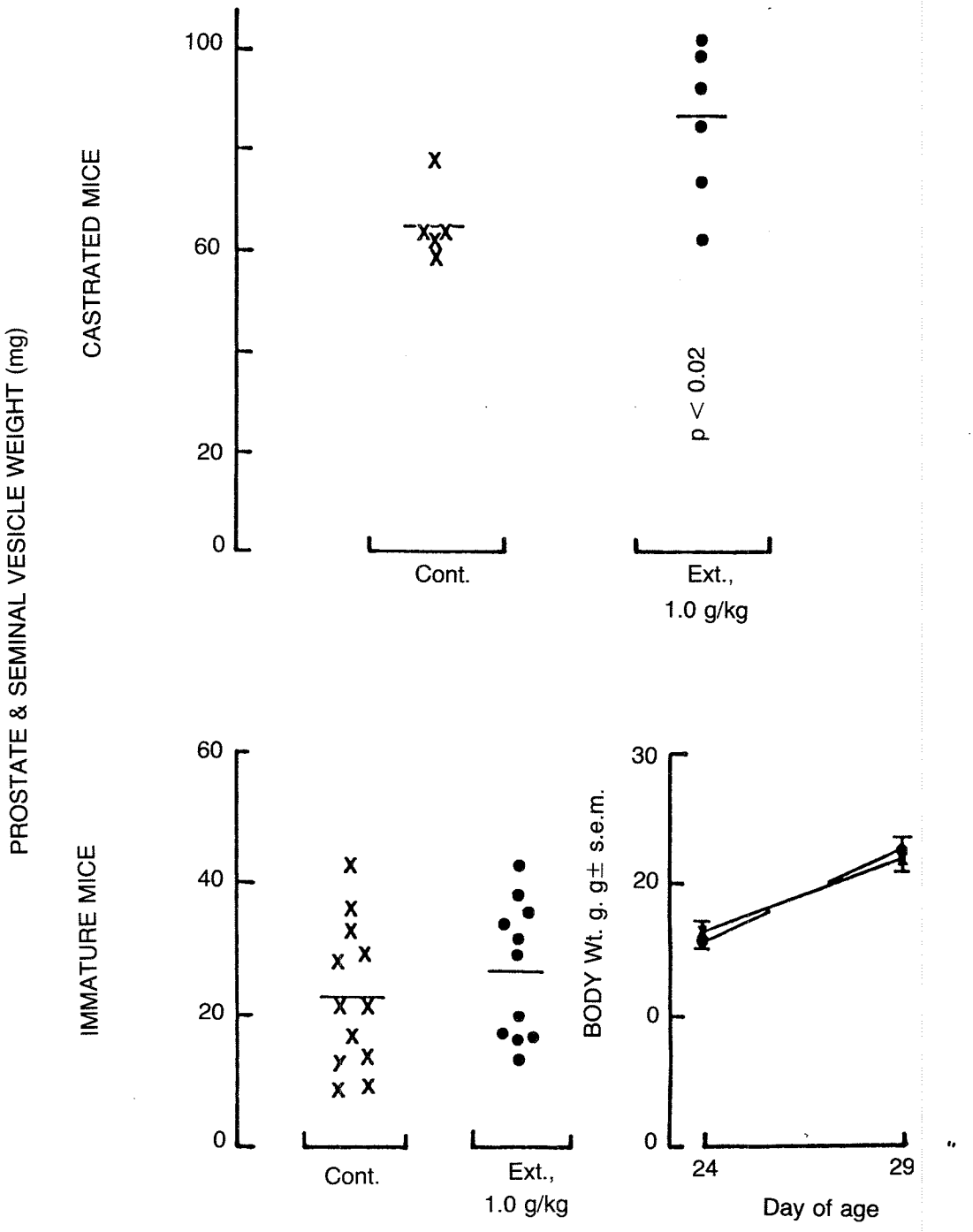

Fig. 4: Effect of extract administration (1 g/kg, orally for 5 days) on the weight of prostate and seminal vesicle of mature (castrated) and immature (24 days old) mice; as well as on body weight of immature mice during the treatment period.

PART FOUR

MEDICAL MIRACLES IN QURAN

CHAPTER I
PAPERS PRESENTED

1. TREATMENT OF ADDICTION BY MEDICATED PLACEBO *(Not available in English).*
   Dr. Y. N. Khawaji and Dr. A. A. Wafa
2. A STUDY OF SERUM AND URINE OSMOLALITIES DURING RAMADAN FASTING *(Not available in English)*
   Dr. M. J. Al-Habbal
3. HONEY APPLICATION IN CANCER WOUNDS *(Not available in English)*
   Dr. O. Raslan
4. HONEY EFFECTS ON SURGICAL WOUNDS *(Not available in English)*
   Dr. Mohammad El-Banby
5. EARLY LIFE PRAYING PREVENTS BACKACHE *(Not available in English)*
   Dr. B.A.M. Kasem
6. SOME ADDITIONAL PAPERS AND DISCUSSIONS *(Not available in English)*

PART FIVE

CLOSING SESSION

CHAPTER I
RECOMMENDATIONS

(Not available in English)

PART SIX

TECHNICAL INDICES

Part Six: *Technical Indices*

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In the Name of Allah the Beneficient, the Merciful

ANNOUNCEMENT

The Islamic Organization for Medical Sciences Invites Nominations for Prizes to be Awarded By THE KUWAIT FOUNDATION FOR THE ADVANCEMENT OF SCIENCES

The Kuwait Foundation for the Advancement of Sciences (KFAS) has instituted two prizes to be awarded every alternate year to support and promote scientific research in the field of Islamic Medical Sciences in the following areas:

1) Medical practice, addressing professional, clinical and laboratory experiments undertaken should be well documented.

2) Appropriate documentation of Islamic Medical Heritage including Medical Islamic Jurisprudence.

Nominations for Prizes are subject to the following:

1. Documents submitted to KFAS should be original, published and academically significant in the field of Islamic Medical Sciences.

2. Nominations proposed by universities, scientific institutes, international organizations, individuals, past recipients of the prize and academic bodies are invited.

3. Closing date for acceptance of Nominations and/or Applications including Nominee's Curriculum Vitae and all supportive documentation is Oct. 31, 1989.

MAILING ADDRESS
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P.O. Box 25263 - Safat
13113 - Kuwait
Telex: 44160 KEFAS

Each Prize consists of a cash sum of KD. 3000/- (KUWAITI DINARS THREE THOUSAND), a KFAS shield and a Certificate of Recognition.

Winners will be invited as guests of KFAS to receive their prizes at the Prize Awarding Ceremony to be held in Kuwait.

The decision of the KFAS Committee in awarding these Prizes is final. Documents submitted for nomination will not be returned.