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Vol. 4

Proceeding of
The Fourth International Conference on

Islamic Medicine

No. IV

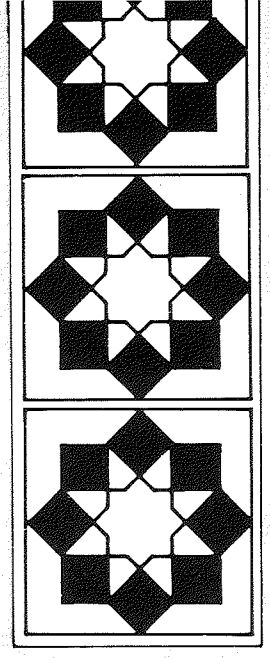
Applied Research

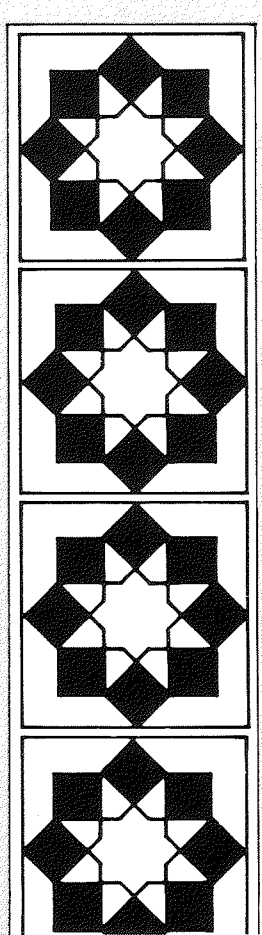
Supervised by
H.E. Dr. Abdul Rahman Abdulla Al-Awadi

The Minister of Public Health
and
President of Islamic Organization
for Medical Sciences

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

Rabi' I 1407/November 1986
State of Kuwait





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PART TWO

APPLIED RESEARCH
A-PROHIBITION AND RESERVATION IN ISLAM

CHAPTER I

PLENARY LECTURE

REPORT ON THE FIRST SESSION

The session was chaired by Prof. Dr. M.A. Kazi, co-chaired by Dr. Khushnood Ahmed Siddiqui and moderated by Dr. Abdussattar Abu Ghuda.

The plenary lecture was delivered by Shaikh Mohd. Al Habib Ibn Al-Khoja entitled "Hermaphrodites between jurisprudence and medicine". The other speakers were scheduled for this session. One speaker Maj. Gen. (Rtd.) Dr.M.I. Burney did not attend and his paper entitled "The rabies problem: epidemiology, prevention and control" was presented by Dr. Abdul Ghafoor. The second paper by Dr. Farooq Messahel entitled "Prohibition of dogs in Islam" was not presented. However the third paper by Prof. Dr. Abdul Hafiz Helmy Mohammad entitled "The dog's zoonotic diseases and community hygiene — an Islamic epidemiological study" was presented as per the schedule.

At the end of lectures, the Chairman invited questions, remarks and comments from the audience. Over 175 scholars were present in the session.

— Editors

CHAPTER II

(a) DOG: ITS HARMFUL EFFECT

PAPERS PRESENTED:

1. THE RABIES PROBLEM: EPIDEMIOLOGY, PREVENTION AND CONTROL
   Maj. Gen. (Rtd.) Dr. M.I. Burney, *et al*
2. PROHIBITION OF DOGS IN ISLAM *(Not available in English)*
   Dr. Farooq Messahel
3. THE DOG'S ZOONOTIC DISEASE AND COMMUNITY HYGIENE - AN ISLAMIC EPIDEMIOLOGICAL STUDY *(Not available in English, but its Abstract included)*
   Prof. Dr. Abdul Hafiz Helmy Mohammad
4. SUMMARY OF DISCUSSION

THE RABIES PROBLEM
EPIDEMIOLOGY, PREVENTION AND CONTROL

Dr. Mohammad Ilyas Burney
and
Dr. Faiyaz Ahmed Lari

PAKISTAN

Rabies a viral zoonoses and a disease taking heavy toll of life is virtually distributed all over the world. The disease maintained in canines and wild life is transmitted to farm animals and to man. The most important role of transmission to man and domestic animals is played by dogs.

Incidence of the disease is not only high but as a whole on the increase. Human fatality rate in the absence of post exposure prophylaxis is 100 per cent. Authentic and reliable statistics, specially for the countries of Asia and Africa, where almost all the Muslim countries are situated, are not available.

World Health Organization has been undertaking world survey of rabies for nearly two decades since 1962. Pertinent data collected from the survey records, reports of PAHO/WHO Epidemiological Surveillance of Rabies for the Americas — Pan American Zoonoses Centre and report of WHO Collaborating Centre for Rabies Surveillance and Research, Tubragen, Federal Republic of Germany and other sources relating to the incidence of disease in man, canines, wild life and farm animals in respect of nearly 100 countries of Americas, Europe, Asia and Africa have been summarized in unpublished WHO document **VPH 83.43.**

Australia, Newzealand, most islands of Oceania and Carribean and some countries e.g. Sweden, Jamaica etc where rabies has been eradicated are free from the disease (WHO, 1982). In Canada and USA there are very few cases of rabies in human since the disease in dogs have been eliminated but on the contrary the disease in wild life is posing a serious threat. In Latin American countries, in the absence of proper control measures the incidence of human rabies is 1.1%. The annual average number of human cases reported for the decade 1970-80 was 280. In the transmission of the disease, dogs and wild life are involved and dogs are playing a major role, incidence of the disease in the animal being 76.5%. There is a long list of wild life involvement in the transmission of disease, most important being the Vampire bats. The wild life species transmit the disease, in majority to the farm animals which constitute 14.8% of the total rabies cases. Rabies in the farm animals constitute a serious loss to livestock. As a whole rabies continues to be a major problem in Americas and the disease has not decreased.

In Europe during the period 1977-81 only 23 human cases are recorded. The prevailing type of disease in Europe is that of wild life and main vector species is red fox (*Vulpes vulpes*) and other animals are secondarily involved. Control of wild life mediated rabies in Europe has not been satisfactorily attained.

In the absence of complete and reliable data on rabies situation in the countries of Africa and Asia, specially of the Muslim countries, it seems difficult, indeed, to make observations with certainty on the

incidence and epidemiological situation of the disease. However taking into consideration the data presented in WHO document **VPH 83.43,** inspite of being far from complete, and based on available informations from other sources in some countries of the region, it can safely be argued that the incidence of human cases of rabies in the countries of Asia and Africa are alarmingly high. There seems to be considerable under reporting of rabies from the African as well as from the countries in Asia. However estimated annual human rabies mortality rates in African countries are within the range of 0.04 to 0.38 per 100,000 inhabitants. In the north, east, west and central African regions dogs are responsible for persistance and transmission of the disease whereas in the south African republics wild life animals play important role in the epidemiology of the disease. However overall dogs involvement in transmission of the disease is 68.6%. Incidence in the farm animals, inspite of under reporting due to lack of diagnostic facilities is quite common and high e.g. in Egypt, Sudan, Tunisia and Morocco 7 to 17% of farm animals are rabies infected.

The rabies problem in Asian countries is one of oldest in the world and the situation in most of the countries, where measures to control the disease have not been properly taken, is worst. The incidence in man as well as in the canines and farm animals is very high. In India approximately 3 millions people receive post exposure treatment consuming more than 35000 litres of vaccine. In Pakistan nearly 60,000 dog bite cases report to hospitals and dispensaries for post exposure prophylaxis, although a fairly large number of cases do not report to hospitals for treatment and thus the exposures must be assumed to be higher than reported. Human rabies deaths, although not exactly known, in India, are estimated to be nearly 20,000 annually. This is the highest figure that has been quoted for any country. Estimated annual human rabies mortality rates in Asia are within the range of 0.05 to 3.3 per 100,000 inhabitants. There are evidences that there is a general increase in the dog bite cases and the incidence of human rabies. In Pakistan during the decade there has been nearly three fold increases in the number of cases of post exposure prophylaxis of man. Rising trend in incidence of human rabies is evidenced in other countries also e.g. India, Indonesia, Philippines.

In almost every country in Asia dog is the main vector species and overall more than 90% dogs are involved in the maintenance and transmission of the disease. Dogs population in the countries are running into millions in the countries burdened with high human population density. It can be safely assumed that dog human ratio in the countries may be 1:10. In Thailand 60% suspected dogs brains, 30% cats brains are shown to be positive and canine rabies incidence is 5000 a year.[1] In Pakistan more than 97% of the biting exposures are due to dogs of which nearly 40% are estimated to be rabid.[2]

Incidence of rabies in farm animals in Asia is quite high. In India and Pakistan thousands of litres of rabies vaccine are produced annually for post exposure prophylaxis of the farm animals viz. cattle, buffaloes, horses etc victim of canine bites. Records of Veterinary Hospital, Lahore provide information on rabies deaths in horses, donkeys, cows, buffaloes, goats and sheep.[3]

PREVENTION AND CONTROL OF RABIES

It is of paramount importance that the clinical rabies in man which is invariably fatal is prevented in the exposed persons. In the Asian and African countries where rabies is endemic and canine rabies is uncontrolled, each and every canine bite must be considered exposure to rabies and resorted to proper first aid and systemic treatments as outlined in WHO's Guide for Post Exposure Treatment[4]. Post exposure treatment is a matter of case management. First aid treatment, viz washing and flushing of the wound(s) as outlined in the guide is the first step which should not be overlooked or ignored. It is initial supplement to systemic treatment — passive and active immunization with rabies immunoglobulin and vaccine. In Pakistan through use of poster, publicising the guide in language of masses, vaccine treatment failure rate have been brought down and efficacy rates increased.

Since Pasteur treated the first human exposure in 1885 nervous tissue vaccines and their modifications introduced by Fermi (1908), Semple (1911), Hempt (1925) and Fuenzalida and Palacios (1953) requiring 14-21 injections are being used inspite of serious inherent drawbacks and limitations. Semple type vaccine is extensively used in Asia and Africa inspite of frequent treatment failures and neuroparalytic reactions. Duck Embryo Vaccine introduced in 1956, though safer than brain tissue vaccine has been used for nearly 30 years in USA, Western world and limited quantities in the developing countries. Its comparative poor immunogenicity and high cost for developing countries of Asia and Africa were the limitations.

The development of tissue culture rabies vaccine and ideally Human Diploid Cell Vaccine (HDCV) which is highly immunogenic, safe and stable, is a major step forward for protection of man from rabies. Since its successful trials[5,6] the vaccine is being successfully and effectively used for the last ten years. The present day high cost of the vaccine is beyond the financial resources of the developing countries in the vast areas of Asia and Africa with their teeming millions under the high risk of the disease. A full course of vaccination with Semple type nervous tissue vaccine (NTV) costs in Pakistan US$ 1.70 as compared to US$ 103 with Human Diploid Cell Rabies Vaccine (HDCRV). More or less similar situation exists in India and other neighbouring countries in Asia.

In comparison to neural tissue vaccine which is being largely used in the third world cost of Human Diploid Cell Rabies Vaccine (HDCRV) is extremely high since diploid cell production is long and difficult and yield of rabies virus from the cells are limited which result in heavy cost of production. To provide cheaper, stable, safe and potent tissue culture rabies vaccine to the developing world intensive efforts have been made to develop new vaccines using alternative cell culture system, different virus strains and new technologies including genetic engineering.

Other tissue culture vaccines that have been developed and are being studied for comparative efficacy and cost effectiveness are Primary Hamster Kidney Cell Rabies Vaccine (PHKCRV), Fetal Bovine Kidney Cell Rabies Vaccine (FBKCRV), Purified Chick Embryo Cell Rabies Vaccine (PCECRV) and Purified Vero Cell Rabies Vaccine (PVCRV). Preliminary studies have shown to be promising and newer purified vaccines may be as good as HDCRV.

Researches on role of interferon, cellular immunity on reduced schedule of immunization and use of lesser quantities of antigen (vaccine) are also being carried out.

For the developing countries of Asia and Africa and specially for the Muslim countries in the regions with limited financial resources it is a challenge. The lives of the Muslim Umma'h has to be saved. Safe, potent tissue culture vaccine has to be provided. Possibilities for development of local facilities for tissue culture vaccine production should be exploited. Pakistan is going to take a lead to establish Tissue Culture Rabies Vaccine Production Laboratory initially to meet its own requirements and later for the brotherly Muslim countries at a much lower cost.

With the development of local facilities for production of safe, potent and cheaper rabies vaccine pre-exposure immunization of the human population at risk on larger scale will be cost effective and a step forward towards the immunological control of the disease in the human population. Availability of low priced, safe, potent and highly immunogenic tissue culture vaccine will pave way for local production of human origin immunoglobulin (RIGH) which again will be cheaper.

Experience in USA, Canada, Europe and some of the countries in the Carribean, Asia and Africa, though very limited in number, has shown that the real and effective control of rabies in human population can be achieved by control of rabies in Canines specially the dogs being involved in more than 90% cases in Asia.

Malaysia is an Asian country and predominantly Muslim. Compulsory vaccination campaign of owned dogs and destruction of all stray dogs started in 1952 eradicated the disease from the country by 1955-56. Since then only 26 confirmed cases of rabies in dogs, one in cat, one in goat and 10 humans have occurred on the Thailand border. Japan, Hong Kong, Taiwan, Israel are the other Asiatic countries where the disease has been controlled.

In view of the magnitude of the human rabies problem basically dependent upon the relationship of dogs to people, WHO's Expert Committees on Bacterial and Viral Zoonoses[7] and on Rabies[8] outlined the plan of control of zoonotic diseases and rabies. The Guidelines for dog rabies control (unpublished WHO document **VPH 83.43**)[4] describe in detail canine rabies situation, urban and rural dog population and on the practical side field techniques, management procedure and legislative provisions for national programmes for canine rabies control.

According to Recommendations of WHO Expert Committee there are five basic elements to any programme of rabies control in dogs and other domesticated animals and they are (a) epidemiological surveillance (b) community education and participation, (c) immunization, (d) dog control and (e) organization and implementation.

The most important element in rabies control in Asia and Africa and the Muslim countries is the dog rabies control. On the basis of their relationship to human society the dog population is divided into three groups viz. (1) owned dogs, (2) community dogs and (3) stray dogs.

It should be obligatory for owned dogs to be vaccinated through persuation, health education and/or legislation. In Pakistan most of the countries farmers, villagers and nomad population own the animal for watch and ward purposes. Very often they get infection from wild canines. Vaccination is only answer and large scale vaccine production is needed for attainment of the required coverage.

Community dogs have no ownership but at the same time they are accepted by the community and for their vaccination or destruction is the choice.

Stray dogs are the bulk of the dog population. According to some estimates 3% of the normal stray dogs harbour the virus. Complete elimination and destruction of stray dogs is required.

The rabies control programme in every country must have popular support, health education, community participation and legislative backing.

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THE DOG'S ZOONOTIC DISEASES AND COMMUNITY HYGIENE — AN ISLAMIC EPIDEMIOLOGICAL STUDY

Prof. A.H. Helmy Mohammad

KUWAIT

ABSTRACT

The dog harbours numerous parasites, about fifty of which are zoonotic, causing human diseases. Of particular importance are: rabies, cutaneous and visceral leishmaniases, hydatidosis, coenurosis, dipylidiasis, sparganosis, cutaneous and visceral larva migrans, pulmonary dirofilariasis and ocular dirofilariasis. Death, splenectomy, amputation of limbs, blindness, enucleation of eyes and severe nervous and other symptoms are among the serious consequences.

In addition to human fatality and disaster, some of the causative organisms cause great economic loss through diseases they produce in domesticated animals. For apparent reasons some of the diseases are treated in greater detail, including parasitological, pathological and epidemiological aspects, as well as recommended preventive measures, prevalence and distribution in many Arab and Moslem countries.

The dog's diseases transmissible to man are anthropozoonotic; in most of them man is an intermediate or accidental host in a dead-end route of infection, while the dog is an important definitive or reservoir host. Some of the diseases are occupational, affecting shepherds and their families, veterinarians, laboratory assistants...etc, but people other than those possessing dogs or getting into direct contact with them are also at high risk. Unfortunately children are particularly vulnerable.

According to Islamic-Law possession of dogs is prohibited; permission is only exceptional and strictly limited. The price of dog is forbidden. Hanbalites and Shafites regard even the live dog as "filth" *(najas)* i.e., inherently filthy *(najis).* Hanafis rule that the dog's saliva is filthy. Allah's Messenger (ﷺ) gave command of killing stray, rabid, ferocious and useless dogs, and warned people that Angels of Mercy would not visit a house sheltering a dog. All these measures and trends tend to effectively reduce the density of dogs' populations beyond levels suitable for epidemiological spreading. Where Moslem and non-Moslem urban populations live symmetrically the preventive value of Moslem conduct and traditions proved itself. Some European capitals still suffer badly of visceral larva migrans in children due to common keeping of pet dogs.

In any preventive health scheme, education should play an important role. In Moslem countries enlightening the public about the great hazards of keeping dogs and the rules and teachings of Islam (shamefully unknown or ignored by many) concerning this practice will prove most effective.

SUMMARY OF DISCUSSION

Prof. Dr. Abdussalam submitted a foot note to Dr. Ghafoor's presentation whereby he discussed the difficulties in getting reasonably economical vaccine. However, he said, that, genetic engineering has provided the alternative which is being done by incorporating the genes of rabies virus to vaccinia. Secondly, rabies and hydatidosis are the most important problems and he emphasized that control of dog population is most suitable alternative. However, this is purely an administrative problem.

Dr. Ahmed Shawki Ibrahim remarked that in Sunna, Fiqh and Holy Quran it is mentioned that whoever has a dog will have his dues cut down. The Western countries will think that Islam is cruel to animals but Quran says save the dogs. Then he told a story related to Prophet Mohammad (ﷺ) about the dog and told his companions not to kill the dogs.

Dr. Najeeb enquired that one of his relations has one dog which weighs one Kg and eats chocolates. Whenever he visits his house the dog licks him. Is it an impurity?

Dr. Mohammad Hasan El-Hefnewi remarked that scientific research should be based on Sunnah and Fiqh. If people do not clean their dogs and they get the disease which comes in the hair then it is endemic though it may be widely prevalent. Bronchial asthma comes from dog skin. This is an example where Fiqh preceded science.

Dr. Mohammed Shoaib Akhtar suggested that we should have some alternative for breaking the life cycle of parasitic disease. While Dr. Ghafoor had no comment on this suggestion, Prof. Helmy commented that Western specialities also commend the Islamic wisdom and killing of stray dogs is being adopted in the West.

CHAPTER III

(b) PORK CONSUMPTION: ITS RELATION TO HEALTH

REPORT ON THE SECOND SESSION

The session was chaired by Prof. Dr. M.D. Shami, co-chaired by Prof. Dr. Mohd. Hassan El-Hefnawi and moderated by Dr. Mohd. Suleiman Al-Ashqar.

Three speakers namely - Dr. Sufian M. El-Assouli, Dr. Amin A. Nanji and Prof. Dr. M. Abdussalam respectively presented their papers on ''Non-infectious diseases associated with pork diet consumption'', ''Pork, alcohol and disease'' and ''Health aspects of the consumption of pig meat'' as per schedule.

Over 150 scholars attended the session. At the end of the lectures, the chairman invited the comments, remarks and questions from the audience.

-Editors

NON-INFECTIOUS DISEASES ASSOCIATED WITH PORK DIET CONSUMPTION

Dr.Sufian M. El-Assouli

and

Dr. Mohammed A. Albar

SAUDI ARABIA

FAT AND CANCER

During the past five decades, the influence of dietary fat on the development of certain forms of cancer has led to the conclusion that there is a good positive correlation between the dietary pork fat consumption and cancer rates of the colon, breast, prostate, endometrium, pancreas, and of the biliary system.

These correlations have arisen from three kinds of evidence. First, descriptive epidemiologic studies which focus on the effect of fat, especially lard, on cancer incidence and mortality rates among different countries and among population groups who have different fat intake and different dietary habits such as the Seventh-Day Adventists. Second, evidence came from experimental studies. These experimental studies have been assisted by the discovery of several animal models in which a lesion mimicing human lesions can be induced chemically. In these models, animals which have been fed a high lard diet developed more colon and breast tumors than animals fed low lard diets.

Third, strong evidence relating the etiology of the above-mentioned cancer to lard came from migrant studies. Within two to three generations, Japanese migrants to the U.S.A. experience an increase in cancer incidence rates. Breast cancer in Japanese-American women had risen to five times that of age-matched native Japanese women during the years 1969-1971. The same is true for the Police immigrants to the United States. These migrant studies exclude the possibility of genetic variations.

Current evidence indicates that the possible mechanisms by which dietary pork fat could play a promoting effect in human carcinogenesis could be through: 1) its effects on the production, activation, or inactivation of carcinogens by the intestinal flora, 2) its effect on the endogenous production, activation, or inactivation of carcinogens or 3) its effect on tissues to alter their susceptibility to carcinogenesis.

Correlation studies between different sources of fat and breast cancer concluded that the highest positive correlation was found for pork fat, followed by other animal fat intake and that a similar association could not be found for vegetable fat.

DIETARY FAT AND COLON CANCER

Cancer of the colon has been the subject of several epidemiologic, migrant, and experimental studies.[1,2,3,4,5] The highest incidence rates are found in North America, New Zealand, and Western Europe (Fig. 1). The lowest incidences are found in Africa, Asia, and Latin America.

Epidemiological studies have shown food preferences, especially fat, to be associated with high- and low-risk populations. Such correlations between fat intake and colon cancer mortality is supported by experimental evidence from animal models. [6, 7] A worldwide correlation between colon cancer incidence and total fat consumptions has been established (Fig. 2).

Migrant studies have shown that Japanese migrants to the U.S.A. experience an increase in colon cancer incidence rates from those rates common in Japan. This observation suggests that environmental factors, rather than genetic characteristics, account for a substantial part in the etiology of colon cancer.

Comparative studies to search for factors that link the foods of individual groups within a small geographical area to their colon cancer risks indicated that the Seventh-Day Adventists, who do not consume pork and adhere to a vegetarian diet have 30-40% less colon cancer death rate of a comparable general population sample. [8, 9]

Similarly, the incidence of colon cancer in Mormons, who eat more whole-grain breads, fruit and vegetables and do not eat pork, also have lower colon cancer than other U.S. white population.[10, 11]

Wynder, et al[12] and others[13], proposed that colon cancer incidence is mainly associated with total dietary fat. Gregor, et al[14] proposed that fat acts as a promoter rather than an initiator during cancer development.

The mechanisms by which dietary fat causes colon cancer has been hypothesized to be as follows: 1) the amount of dietary fat determines both the concentration of acid and neutral sterol substrates in the large bowel and also the composition of the microflora acting on such substrates. 2) The gut microflora metabolizes acid and neutral sterols to carcinogens active in the large bowel.[15] The bacteria alters the structure of colonic steroid[16, 17] and they become potential carcinogenic since their overall structure is similar to carcinogenic polycyclic aromatic hydrocarbons (PAH) and they may be converted chemically to 3-methylcholanthrene. Also, human gut flora have been shown to achieve partial aromatization of the sterol ring system, and full aromatization of the bile and nucleus would yield a carcinogen metabolite. Such microflora-mediated reactions are unlikely to yield polycyclic aromatic hydrocarbons from bile-salts but are more likely to yield products that act as colon tumor-promotors or co-carcinogens rather than as complete carcinogens.[18]

Thus, a high-fat diet may not only change the composition of bile acids but also modify the activity of gut microflora which may,in turn,produce tumor-promoting substances from bile acids in the lumen of the colon.[19,20]

Additional support to the role of dietary lard in the induction of colon cancer in man came from experimental studies in which intestinal tumors were induced chemically. Animals fed on a high-lard (20%) diet developed more intestinal tumors and more metastasis than rats fed low-lard diets (5%) (Table I).[21]

DIETARY FAT AND CANCER OF THE BREAST

Epidemiological studies have generated hypothesis for the etiology of breast cancer through international comparison of incidence, case-control studies, migration studies and experimental studies. Such studies have provided the basis for the influence of nutrition and fat, in particular on breast cancer incidence.

High breast cancer incidences are found in the U.S.A. and Western Europe and low rates in Asia, particularly Japan (Fig. 3).

The strongest evidence for environmental factors in the etiology of breast cancer is found in the results of migrant studies. Within two to three generations, Japanese migrants to the U.S.A. experienced an increase in cancer incidence rates from those common in Japan (Fig. 4). During 1969-1971 the incidence of breast cancer in Japanese-American women had risen to five times that of age-matched native Japanese women.[22]

Alterations in dietary practice, especially the increase in pork fat intake, appear to be the factor that best accounts for the increase in breast cancer incidence.

A positive correlation between breast cancer mortality and daily per capita consumption of fat has been demonstrated by a number of researchers (Fig. 5). Hirayama[23] correlated breast cancer incidence in 12 different districts of Japan with specific food consumption patterns. Of the food items studied, the highest positive correlation was found for pork followed by total animal fat intake.

Experimental studies showed that spontaneous breast tumor incidence rates in female DBA mice were higher in those fed an isocaloric high-fat diets than those fed a low-fat diet and through all the experimental studies one point stands out clearly: high intake of dietary fat increases the incidence of mammary cancer in rodents.(Fig. 6)[24]

The possible mechanism(s) by which dietary fat may exert its effect on breast cancer have been postulated by Hopkins and West[25] and others[26, 27] to be: a) direct effects at the level of the mammary gland. These effects are based on the physical and chemical properties of fat, the formation of lipid peroxides, alterations in membrane structure and/or function, and enhanced prostaglandin synthesis. Since polyunsaturated fatty acid (PUFA) is converted by free radical reactions to lipid peroxides, a model involving breast cancer and lipid peroxidation has been advanced. Lipid peroxidation has been associated with a variety of pathological process[28] including mutagenesis and carcinogenisis. It is possible that increased peroxidation of membrane lipids results in alterations in the function of transformed mammary cell membrane which, in turn, permit increased rates of growth[25], or that lipid peroxidation and free radical processes accompanying it are primarily associated with the activation of procarcinogens.[29] Since lard contains 67% polyunsaturated fatty acid, its effect is more prominent in the process of carcinogenesis. b) Indrect effects of fat could be mediated by host systems remote from the mammary gland. In this case the dietary fat secondarily stimulates mammary tumor growth by modifying the physiology of the host through altering the: 1) immune rejection responses, 2) mixed function oxidases, and 3) endocrine control system. Also, fat has an enhancing effect on breast cancer development through altering the circulating prolactin levels but not estrogen levels. Prolactin is proposed to mediate the fat effect by virtue of its duel capacity as a liporegulatory hormone and as a promoter of mammary tumor development.[30]

DIETARY FAT AND CANCER OF THE PROSTATE

Cancer of the prostate is common in the U.S. and western countries and uncommon in Japan and Africa[31] (Fig. 7). One striking difference between diets in high- and low-risk areas is the fat intake (Fig. 8) which accounts for 40% of the daily calories in high-risk areas and 20% calories in low-risk areas.

Clinical studies have shown that the connecting link between dietary fat and the incidence of prostatic cancer is hormonally dependent.[32] Any factor that affects hormonal secretion, retention, and, in particular, the sensitivity of the target organ and/or cells influences the frequency of this cancer.[33] Since fat may modify hormonal systems, it has the potential of inhibiting or enhancing tumorogenesis.

DIETARY FAT AND ENDOMETRIAL CANCER

The incidence of endometrial cancer is highly correlated wth levels of fat consumption (Fig. 9). The incidence of endometrial cancer is also highly correlated with those of breast cancer and colon cancer, which are also both thought possibly to be causally related to fat consumption.[34] Epidemiologic studies have identified the following factors as associated with a high individual risk of endometrial cancer: obesity, early menarche, late menopause, diabetes mellitus, and excessive production of estrogen and all of these factors may be explicable through a common mechanism which is dietary excess of fat.The precise role of estrogens

in the genesis of endometrial cancer is still uncertain. It has been suggested that estrone may be directly carcinogenic.[35] It is possible, however, that excessive endometrial stimulation by estrogens may facilitate the action of other carcinogens. If this is the case and diet is the principal determinant of excessive estrogen production in women with endometrial cancer, then this is another example of an effect of diet on the susceptibility of a tissue to carcinogenesis.

Seventh-Day Adventist women in general (about 50% of whom are vegetarian) have about a 40% lower mortality from endometrical cancer than the general population.[39] This is consistent with the role of fat in the incidence of endometrial cancer.

DIETARY FAT AND CANCER OF THE PANCREAS

Studies on imigrants have provided valuable information on the influence of fat in the genesis of pancreatic cancer. A study on Japanese immigrants to the U.S.A. showed that the standardized mortality rates for pancreatic cancer was higher among Japanese Americans as compared with white Americans. Similarly, the rate incidence of pancreatic cancer among religious groups who adhere to non-pork diets, such as Seventh-Day Adventists, are all in the vicinity of 50-75% of the general rates.[9]

The hypothesis for the etiology of pancreatic cancer by Wynder is that fat causes an increase in bile excretion which, in turn, may contain carcinogens and/or co-carcinogens and promoters and that this bile, refluxed into the pancreatic duct, may cause pancreatic cancer. Also, the effect of fats on the composition of the biliary bile acid have been shown to act as promoters.

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TABLE I. COLON TUMOR INCIDENCE IN RATS FED DIETS HIGH IN FAT AND TREATED WITH CARCINOGENS

Diet fat	Percentage in diet	Protein	Percentage in diet	Carcinogen	Percentage of rats with colon tumors
Lard	5	Casein	25	DMH	17
Lard	20		25	DMH	67

Fig. 1: Age-adjusted death rates for malignant neoplasms of intestine, except rectum, in different countries, 1966-1967. (From Segi and Kurihara, 1972).

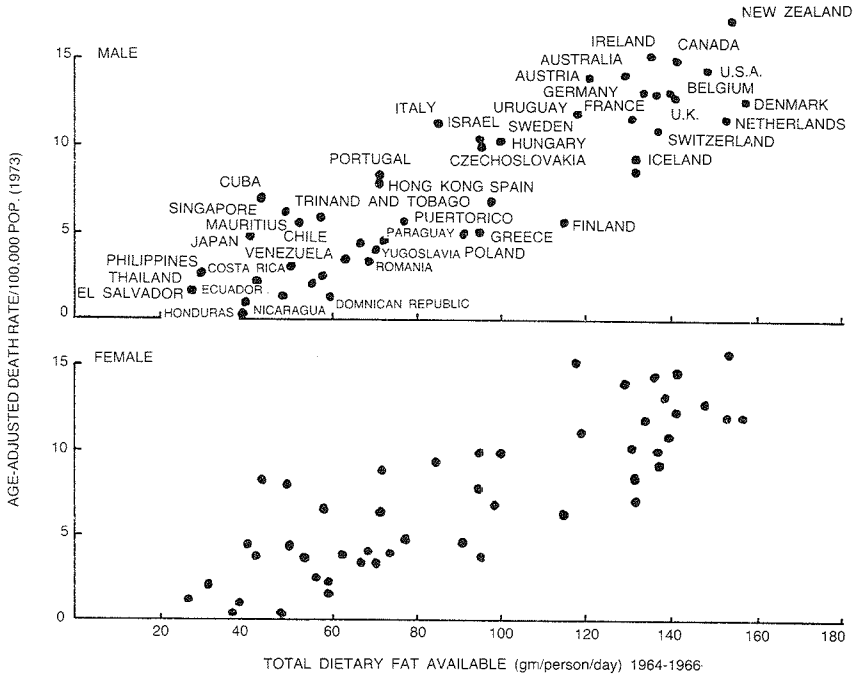

Fig. 2: Correlation between age-adjusted mortality from colon cancer and per capita consumption of fat (From Carroll and Khor, 1975).

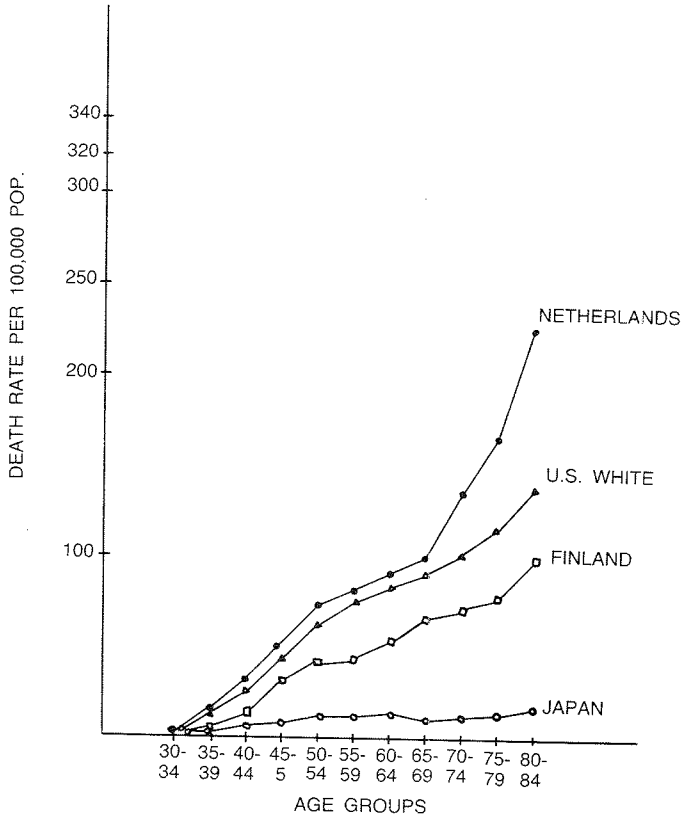

Fig. 3: Female breast cancer death rates by age in four countries, 1966-1967. (From Segi and Kurihara, 1972.)

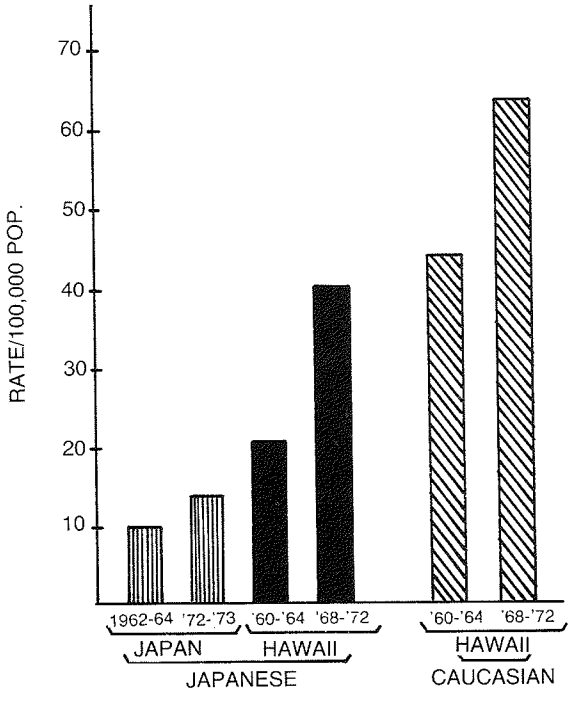

Fig. 4. Age-adjusted breast cancer incidence rates in native Japanese (striped ba Hawaiian Japanese (solid bars), and white Hawaiians (hatched bars). (From Wynder; Harayama, 1978.)

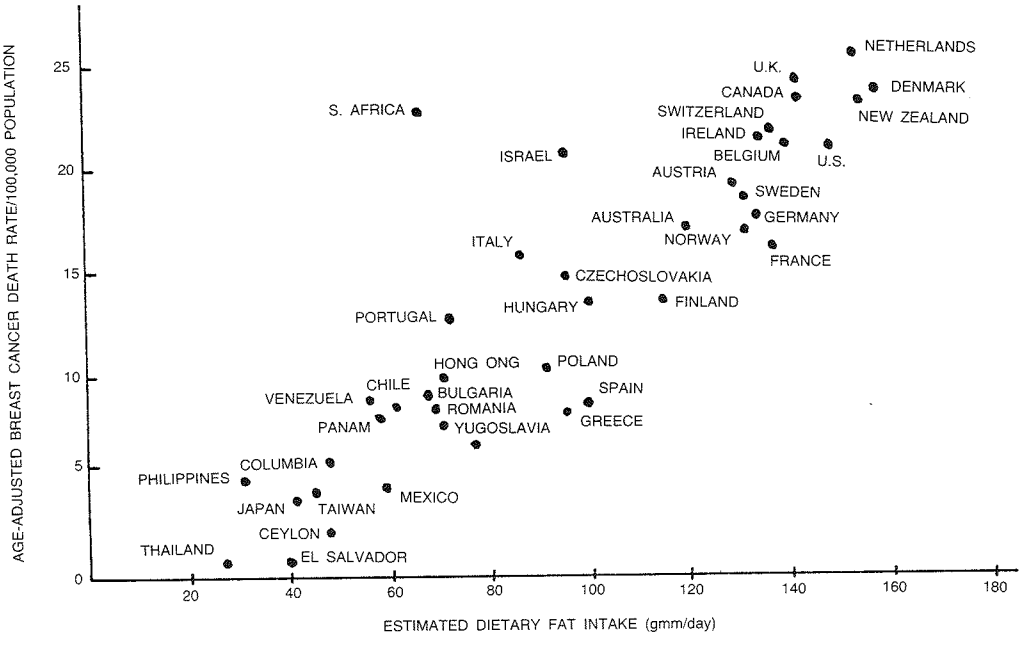

Fig. 5: Correlation between age-adjusted death rates from female breast cancer and per capital consumption or fat. (From Caroll and Khor, 1975.)

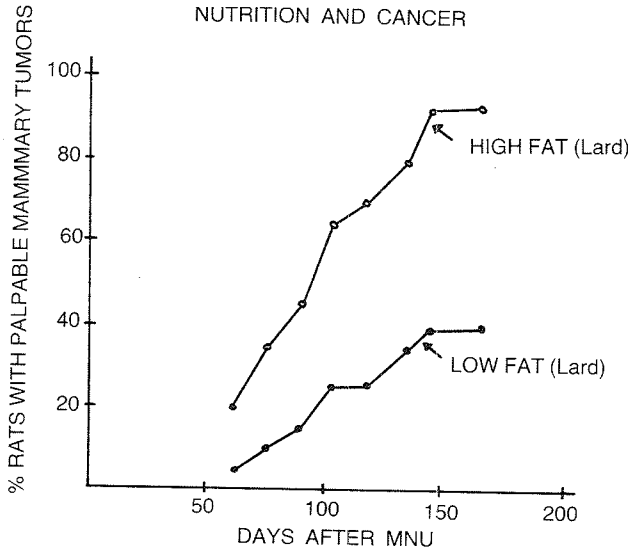

Fig. 6: Effect of high- or low-fat diet on methylnitrosourea (MNU)-induced breast cancer incidence in female F344 rats. MNU was administered intravenously at 55 days of age and the rat was then fed high-fat (20% lard) or low-fat (% lard) diet. The median latent period (time when 50% of tunor-bearing rats had developed tumors) was 83 days in the high-fat group and 103 days in the low-fat group. The tunor incidence differed significantly from the eightieth day on ($P<0.01$). (From Chan et al., 1977.)

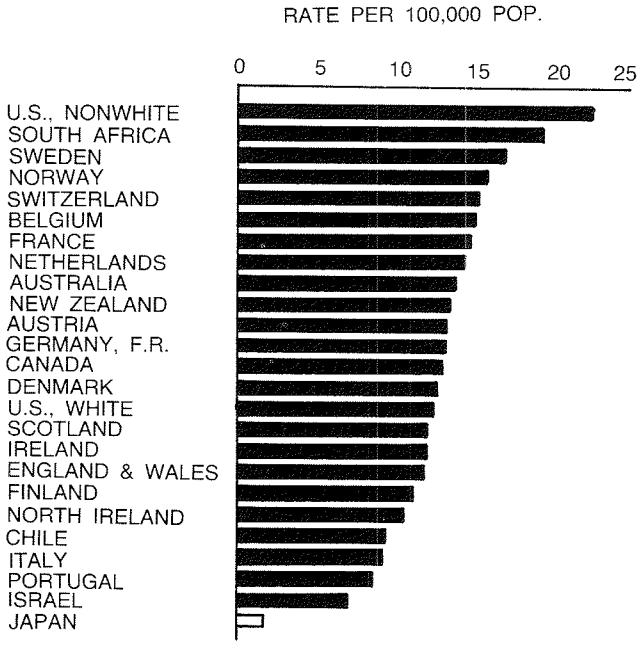

Fig. 7: Age-adjusted death rates for prostate cancer in different countries, 1966-1967. (From Segi and Kurihara, 1972.)

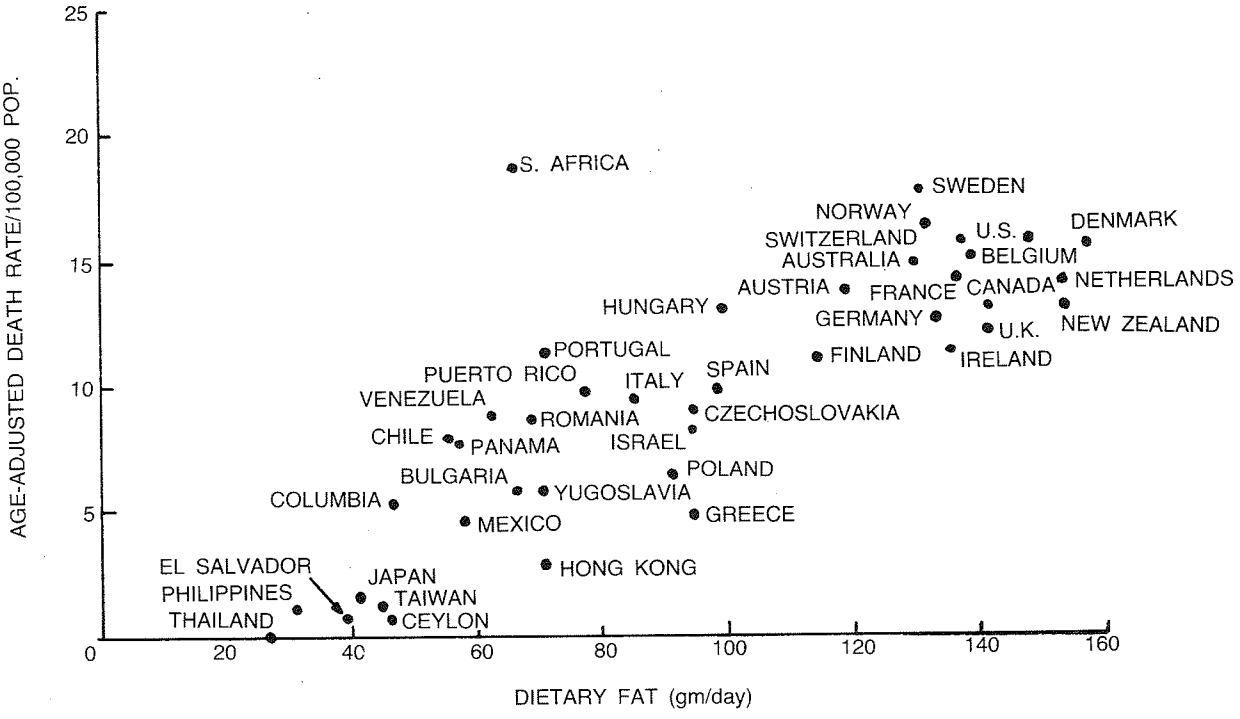

Fig. 8: Correlation between age-adjusted death rates from prostate cancer and per capita consumption of fat.

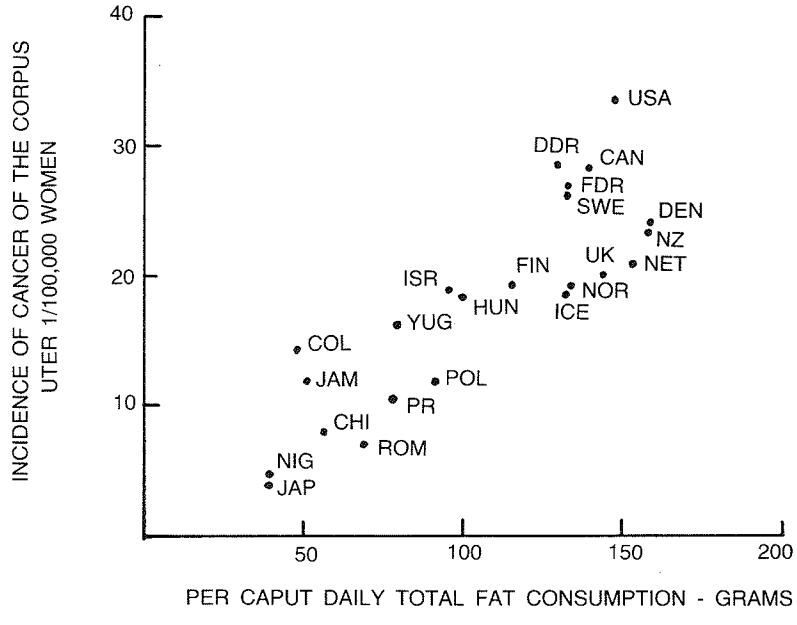

Fig. 9: Correlation of national fat consumption levels with incidence of endometrial cancer in 23 countries (Armstrong and Doll 1975).

PORK, ALCOHOL AND DISEASE

Dr. Amin A. Nanji
CANADA

INTRODUCTION

HE HAS FORBIDDEN YOU DEAD MEAT, AND BLOOD, AND THE FLESH OF SWINE, AND ANY OVER WHICH THE NAME OF OTHER THAN GOD HAS BEEN INVOKED

(S16:V115)

THEY WILL ASK YOU CONCERNING ALCOHOLIC BEVERAGES AND GAMBLING. SAY: IN EACH OF THERE LIES SERIOUS VICE, AS WELL AS SOME BENEFITS FOR MANKIND; YET THEIR SIN IS GREATER THAN THEIR USEFULNESS

(S2:V219)

With the two above Suras, I would like to go through some of the studies which we have carried out to study the interactions between pork and alcohol. These studies include a) pork, alcohol and cirrhosis, b) pork, wine and hepatocellular carcinoma, c) pork and multiple sclerosis, d) pork, alcohol and vascular disease, and e) pork and alcoholism.

(A) Pork, Alcohol and Liver Cirrhosis[1]

The relative importance of nutrition and alcohol in the pathogenesis of alcoholic cirrhosis has been a source of interest and controversy for several years. Dietary fat is one of the factors known to influence the degree of fat infiltration secondary to alcohol abuse.[2] We hypothesized that different sources of dietary fat (e.g. pork, beef) might alter the individual's susceptibility to alcohol. To study this matter further, we examined the per capita consumption of total fat, beef and pork in several countries in relation to the corresponding annual mortality rates of cirrhosis.

Published data for per capita consumption of total fat, pork and beef[3-5] and alcohol consumption[6] were obtained for 16 countries (Figure 1). Consumption of all of the above commodities was correlated with the corresponding mortality rates. The product of pork and ethanol was also correlated with cirrhosis mortality to determine if the combination correlated with cirrhosis better than either pork or ethanol alone. We also carried out the same correlations for the Canadian provinces.

We then restricted the study of 7 countries with a narrow range of alcohol consumption (7.5-11.0 L/capital/yr) and wide range of cirrhosis mortality (Figure 2).

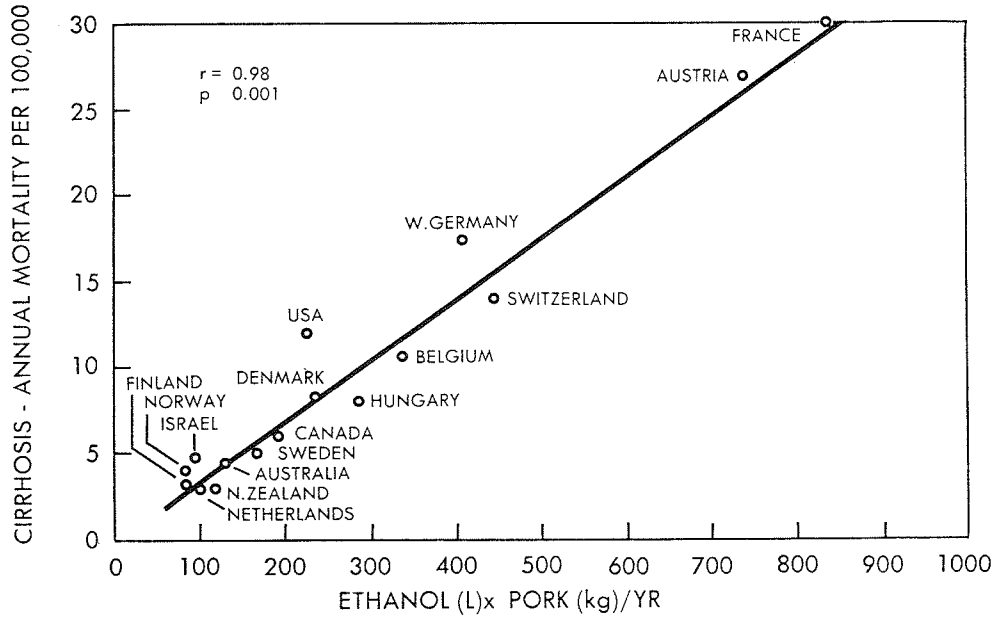

Figure 1

Figure 1 shows the correlation between cirrhosis mortality and the product of ethanol and pork consumption($r = 0.98$, $p < 0.001$).

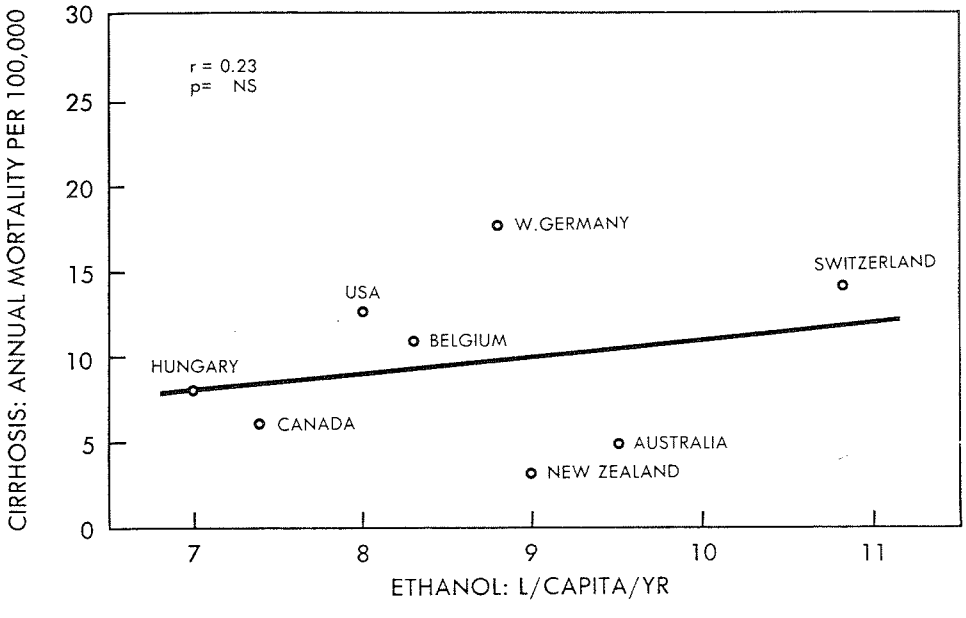

Figure 2

Figure 2 shows no significant correlation between alcohol consumption and cirrhosis mortality for the 7 countries studied.

TABLE I
CIRRHOSIS MORTALITY AND PORK AND ALCOHOL CONSUMPTION IN THE CANADIAN PROVINCES (1978)

Province	Cirrhosis mortality (per 100,000)	Alcohol consumption (1/caput/yr)	Pork consumption (kg/caput/yr)
Prince Edward Island	6.5	11.0	5.8
Newfoundland	10.2	10.68	6.8
Nova Scotia	10.6	10.32	3.6
Saskatchewan	13.4	10.14	4.3
New Brunswick	14.5	9.23	4.4
Alberta	16.4	13.05	5.7
Manitoba	16.6	10.68	6.9
Ontario	18.2	11.50	7.2
Quebec	19.0	10.46	14.9
British Columbia	27.5	12.82	8.4
Correlation with cirrhosis mortality		0.1 (Not significant)	0.60 ($p<0.01$)
Without Prince Edward Island and Newfoundland		0.28 (Not significant)	0.93 ($p< 0.01$)

Table 1 shows the alcohol and pork consumption mortality for the 10 Canadian Provinces. Cirrhosis mortality correlates significantly with pork consumption but not with ethanol intake.

The above correlations between pork consumption and cirrhosis are impressive enough to suggest **that pork facilitates the occurrence of cirrhosis** in individuals who drink alcohol.

(B) Pork, Alcohol and Liver Cancer[7]

The role of dietary fats in the pathogenesis of hepatocellular carinoma is unclear. To study this matter further, we extended our observations linking pork and cirrhosis to the study of HCC.

We correlated per capita consumption of alcohol, beef, pork and cigarettes with corresponding age-adjusted mortality rates from HCC in 18 countries. Since hepatitis B virus is a major risk factor for HCC, we included in our study only those countries where the carrier rate for hepatitis B virus antigen was $< 2\%$.

TABLE 2
RELATIONSHIP BETWEEN MORTALITY RATES PER 100,000 FROM HEPATOCELLULAR CARCINOMA AND PER CAPITA CONSUMPTION OF ALCOHOL (INCLUDING WINE AND PORK)

COUNTRY	Per capita consumption			
	HCC mortality rate per 100,000	Alcohol (L/yr)	Wine (L/yr)	Pork (kg/yr)
Canada	1.4	6.7	3.9	25.7
US	1.5	8.2	4.7	28.1
Japan	1.8	12.9	3.3	11.4
Norway	2.0	3.8	3.6	21.8
United Kingdom	2.5	4.7	3.50	26.0
Sweden	2.6	7.3	6.0	33.5
New Zealand	2.6	9.5	5.1	12.6
Finland	3.0	6.4	3.8	24.9
Denmark	3.3	9.4	5.6	42.3
Switzerland	4.4	11.1	39.5	40.9
Federal Republic of Germany	5.1	13.8	15.9	46.2
Austria	5.6	11.5	29.3	45.4
Belgium	5.7	10.1	13.7	40.7
Czechoslovakia	6.2	11.7	13.8	31.9
Hungary	7.0	12.6	35.5	40.8
France	7.1	16.0	100.8	32.6
Yugoslavia	7.5	6.9	25.3	22.0
Poland	7.7	4.9	5.3	43.5
Kendall Correlation		0.40	0.46	0.40
P value		< 0.5	<0.05	<0.05

Table 2 shows the relationship between mortality rates from HCC and per capital consumption of alcohol, wine and pork. Our observations indicate that **both alcohol and pork are associated with the risk of developing hepatocellular carcinoma.**

TABLE 3
DIFFERENCES IN COMMODITY CONSUMPTION IN COUNTRIES WITH MORTALITY RATES FROM HEPATOCELLULAR CARCINOMA OF LESS THAN AND GREATER THAN OR EQUAL TO 3 PER 100,000

	Countries with HCC mortality 3/100,000* (n = 8)	Countries with HCC mortality 3/100,000 (n = 10)	P
Alcohol consumption (L/capita/yr)	8.4 3.2	19.2 8.8	0.002
Beer (L/capita/yr)	14.6 6.6	18.9 9.8	NS
Wine (L/capita/yr)	1.3 0.97	6.7 6.5	0.01
Spirits (L/capita/yr)	1.0 0.39	1.23 0.4	NS
Fat consumption (g/capita/day)	122 38	107 31	NS
Mean consumption (g/capita/day)	55.6 15.8	46.8 12.0	NS
Pork consumption	23.0 7.6	38.6 7.6	0.001

* Includes Canada, US, Japan, Norway, United Kingdom, Sweden, New Zealand, and Finland.

Includes Denmark, Switzerland, Federal Republicof Germany, Austria, Belgium, Czechoslovakia, Hungary, France, Yugoslavia, and Poland

NS: not significant

Table 3 shows the comparison of the per capita commodity consumption in the groups of countries with the mortality rates from HCC of less than and greater than 3/100,000: only **alcohol (wine) and pork consumption** are higher in the group with higher rates for HCC.

(C) Pork and Multiple Sclerosis

The peculiar geographical distribution of multiple sclerosis (MS) has long been a puzzle to researchers.[8] One of the risk factors for MS is dietary fat. Since beef and pork are major sources of animal fat, the relationship between MS and the consumption of beef and pork was investigated.

The per capita consumption of beef and pork was correlated with prevalence rates for MS. For the purposes of the study, only those countries where case ascertainment was complete were included.

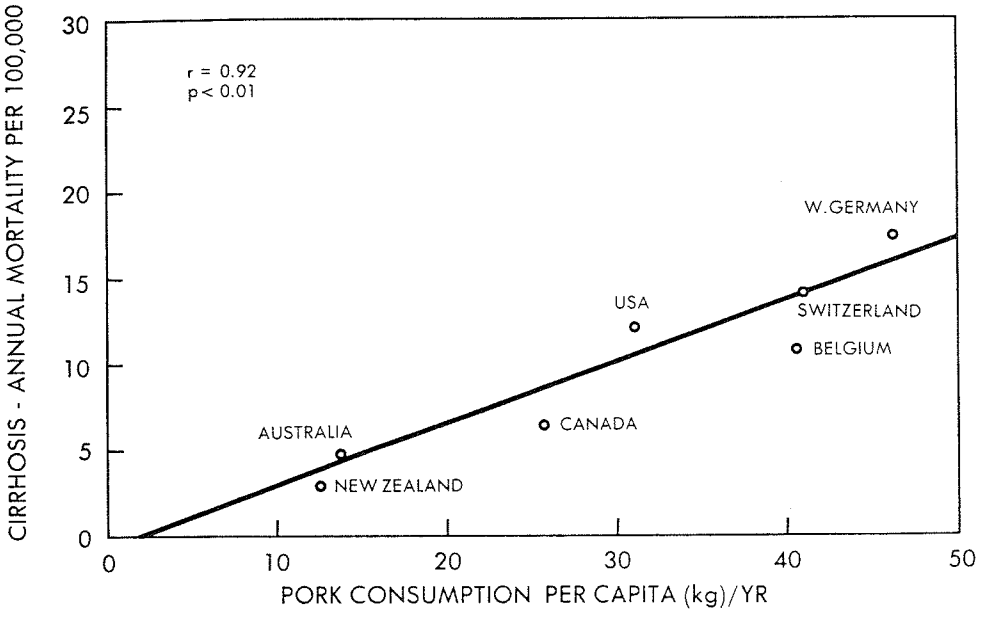

Figure 3

Figure 3 shows that for the same 7 countries, there was a significant correlation between pork consumption and cirrhosis.

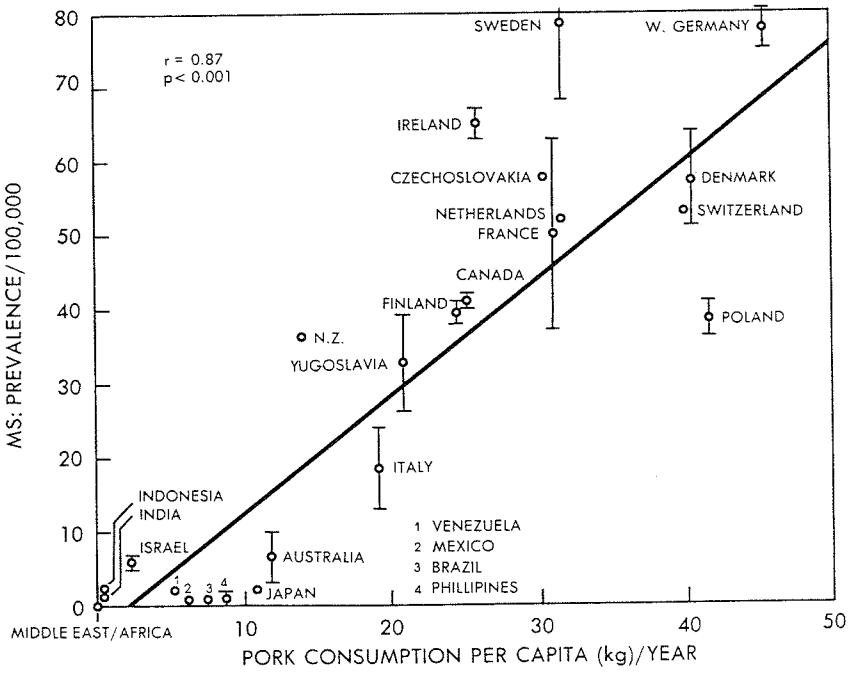

Figure 4 shows the correlation between MS prevalence and pork consumption ($r = 0.87$, $p < 0.001$). Pork consumption also correlated with latitude ($r = 0.82$, $p < 0.001$).

Our observations that pork consumption correlates with both prevalence of MS and latitude might explain why MS is common in temperate countries (e.g. Western Europe) are rare in countries where pork is forbidden by religious customs (e.g. Middle East).[9]

The strength of the correlation between pork consumption and MS prevalence is impressive enough to suggest that **pork increases the risk of developing MS.**

(D) Alcohol, Pork, Beef and Vascular Disease

Population studies of alcohol consumption and coronary heart disease have shown a negative association between mortality due to ischemic heart disease (IHD) and alcohol consumption.[10] One of the problems with correlations between alcohol consumption and mortality from IHD is the latency period between the period of alcohol consumption and corresponding decrease in mortality. To overcome this problem, the mortality from IHD in 27 countries[11] was correlated with the percentage of total alcohol consumption consumed in the form of a particular alcoholic beverage. (wine, beer, spirits).

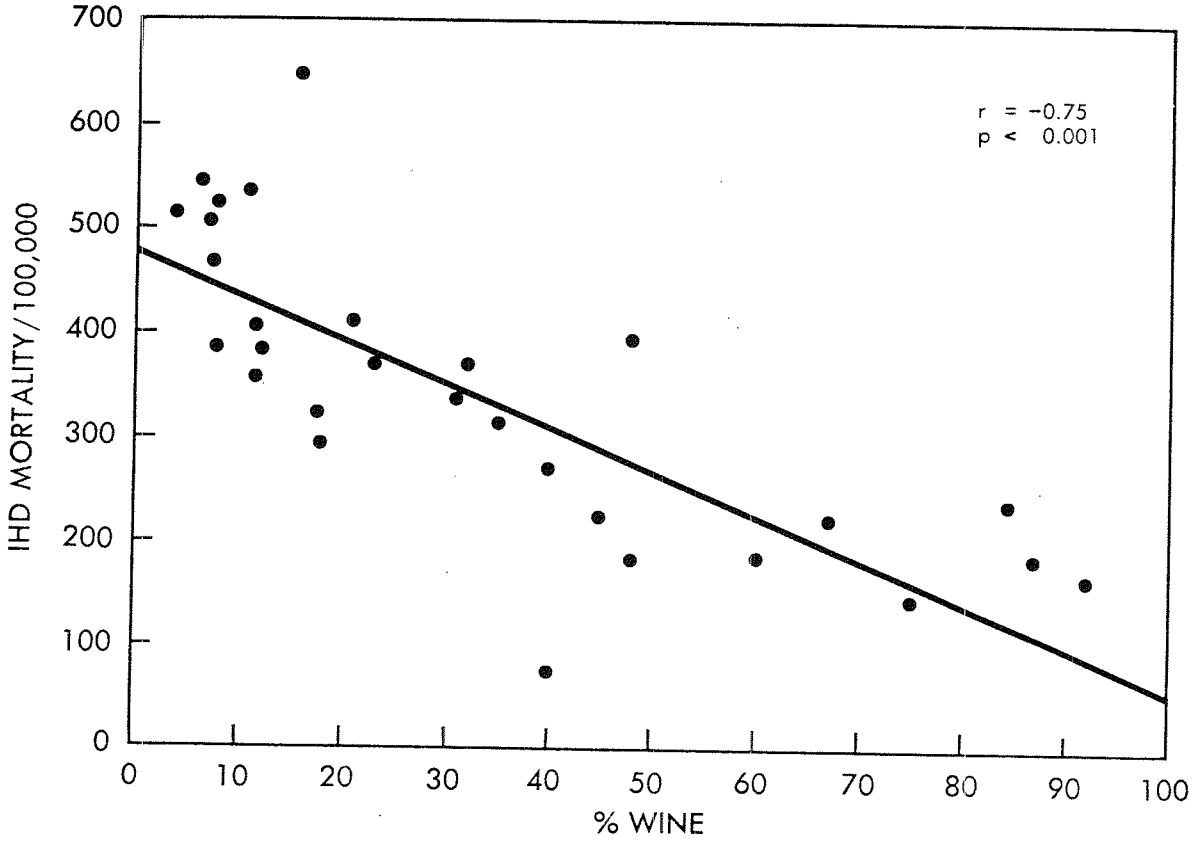

Figure 5 shows an inverse correlation between wine consumption and IHD in the 27 countries. This confirms observations of previous workers.[12]

By far the more interesting correlation to emerge was the positive association between percentage beer consumption and ischemic heart disease.

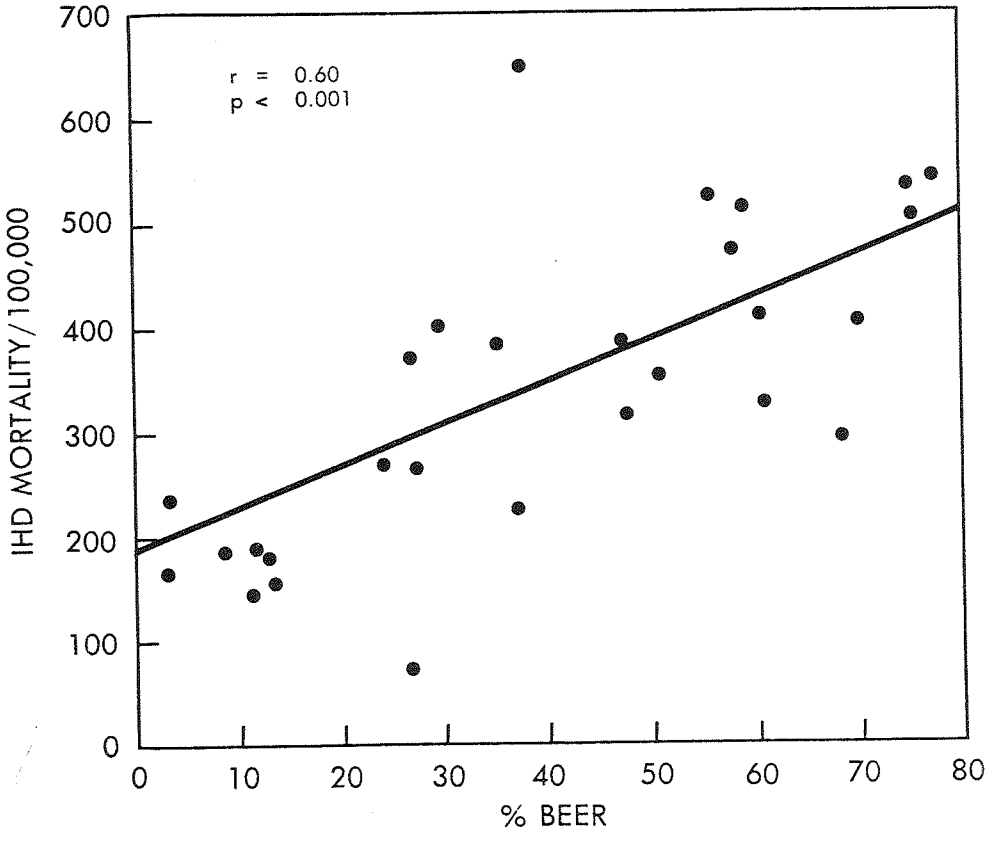

Figure 6

Figure 6 shows the positive association between beer consumption and IHD.

We also studied the annual change (%) in IHD mortality (1970-1980) for 22 countries and correlated this with the percentage change in the consumption of alcoholic beverages.[13] On the basis of previous correlations between alcoholic beverages and IHD, a risk score was calculated for each country.

TABLE 4. ANNUAL CHANGE IN CHD MORTALITY (1970-1980) IN 22 COUNTRIES WITH CHANGES IN ALCOHOLIC BEVERAGE CONSUMPTION.

Country	Annual % change in CHD mortality (1970-1980)		% Change in Consumption (1970-1980)		
		Alcohol (as 100% pure alcohol)	Wine	Beer	Risk Score
United States	−3.0	+44.3	+69	+39	−26
Australia	−2.1	+25.6	+102	+15.5	−67.2
Finland	−1.8	+72.0	+114	+25.0	−70.5
Denmark	−1.7	+41.5	+151	+18.6	−102.0
Belgium	−1.7	+38.5	+51.4	+5.8	−34.2
Canada	−1.6	+46.8	+118	+24	−74.1
New Zealand	−1.2	+38.6	+115	+9.2	−80.8
Norway	−1.1	+35.3	+100	+26.0	−60.1
Netherlands	−0.9	+39.8	+166	+59	−88.0
U.K. (England, Wales)	+0.1	+50.0	+100	+21	−70.0
Switzerland	+0.2	+4.0	+20	−6	−11.4
West Germany	+0.4	+12.3	+61	+9.7	−39.7
Austria	+0.6	+15.8	+22.6	+9.8	−11.0
Yugoslavia	+0.6	+5.7	+9.2	+80.5	+37.0
Czechoslovakia	+0.6	+11.6	+12.3	+6.1	−5.7
Italy	+1.0	0	+11.7	+67.3	+25.3
France	+1.1	−8.6	−5.2	+15.3	+5.3
Sweden	+2.0	+50.0	+50.0	+37.0	−11.4
Hungary	+2.6	+21.0	0	+54.3	+32.6
Romania	+4.3	+31.7	+32.0	+109	+41.5
Bulgaria	+5.6	+31.5	+20.8	+76.0	+30.6
Spain	+6.2	+23.7	+11.7	+47.1	+19.5
T		−0.29	−0.50	0.32	0.67
P		NS	<0.01	<0.05	<0.001

Table 4 shows the change in IHD mortality versus the change in alcoholic beverage consumption. This study adds to previous studies, in that, it suggests other constituents besides alcohol may also play a role in determining risk for ischemic heart disease.

To determine whether the type of alcoholic beverage determined the relative distribution of cerebrovascular disease (CVD) and ischemic heart disease (IHD) we correlated the consumption of alcoholic beverages with the ratio of mortality rates from CVD and IHD.

TABLE 5. RELATIONSHIP BETWEEN CVD/IHD AND PERCENTAGE CONTRIBUTION TO TOTAL ALCOHOL CONSUMPTION BY EACH BEVERAGE

% of Total Alcohol Consumption	CVD/IHD Ratio	
	Males	Females
Beer	−0.69*	−0.75*
Wine	+0.46**	+0.50***
Spirits	+0.23	+0.26
Wine and Spirits	+0.69*	+0.75*
Alcohol (all beverages)	+0.22	+0.25

* $p<0.001$
** $p<0.05$
*** $p<0.02$

Table 5 shows the significant correlations - our results suggest that the relative distributions of CVD versus IHD might be influenced by the choice of alcoholic beverages.

We also carried out a similar study for different types of dietary meat. Our studies indicate a higher proportion of cerebrovascular disease in countries with a higher pork consumption suggesting that pork somehow contributes to the development of cerebrovascular disease.

(E) Does Pork Consumption Lead to Alcoholism?

Given the several studies cited above, the obvious question is: Does pork consumption lead to alcohol consumption. To test this hypothesis, we correlated in 36 countries where figures for both alcohol and pork consumption were available. A significant correlation of $r = 0.72$, $p<0.01$ was obtained. To study whether this relationship held true within a country, we studied the same co-relation in the 10 provinces of Canada. Table 6 again shows a significant correlation between pork consumption and the number of alcoholics in each province. ($r=0.77$, $p<0.01$)

TABLE 6
RELATIONSHIP BETWEEN PORK CONSUMPTION AND THE NUMBER OF ALCOHOLISM

Province	Pork Consumption (kg/caput)	No. of Alcoholics
Nova Scotia	3.6	1900
Saskatchewan	4.3	2650
New Brunswick	4.4	2500
Alberta	5.7	2450
Prince Edward Island	5.8	2150
Newfoundland	6.8	1950
Manitoba	6.9	2900
Ontario	7.2	3750
British Columbia	8.4	3950
Quebec	14.9	4150

The above Table clearly shows the relationship between pork consumption and the number of alcoholics.

SUMMARY

What is novel in the field of pork and alcohol interaction? Our studies show for the first time that these two commodities, prohibited in Islam, may interact to cause disease. These diseases include liver cirrhosis and cancer, multiple sclerosis, cerebrovascular disease and alcoholism. What do we do next? We are in the process of performing animal experiments to determine whether these interactions can be reproduced in the experimental animal. Our studies will, Inshallah, add to our epidemiologic studies linking pork and alcohol to disease states.

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HEALTH ASPECTS OF THE CONSUMPTION OF PIGMEAT (PORK)

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INTRODUCTION

Foods of animal origin such as meat, fish, eggs and milk are an important source of easily digested proteins of high biological value and of some other valuable nutrients. However, large communities of people in different parts of the world avoid one or other type of these valuable foods, and vegetarians reject all of them. One of the meats which is widely and vigorously rejected is pork. Its strict avoidance by Muslims and practising Jews is well known, but other communities in Africa, Central and Southern Asia and Oceania also reject pigmeat (see Simoons, 1961, for a discussion of the cultural geography of avoidance of pork and other flesh foods).[1]

Various theories have been advanced to explain the origin and rationale of avoidance of pork and other foods of animal origin (see Annex). One of the several hypotheses stipulates that the prohibition of pork resulted from a collective experience of disease (or diseases) transmitted or caused by pigmeat in antiquity or ancient times. Various recent findings in food hazards, zoonoses and risk factors related to chronic degenerative diseases have been cited in support of, or against, this theory. Of course, folk medicine and popular food lore of various countries where pork is consumed, are also full of anecdotes ("wisdom") on this subject.

The present paper attempts an examination of the available scientific evidence of the risks to human health associated with the consumption of pork and its products. Where appropriate, a comparison is made with other types of meat, such as beef, mutton, poultry, and fish. The nutritional aspects are referred to only as risk factors where they are hazardous.

Health hazards of pork may be discussed under the following headings:

1. Microbial and parasitic infections transmitted through pork.
2. Non-communicable diseases attributed to the consumption of pork.
3. Risk factors in relation to chronic degenerative diseases.
4. Hazards from residues, and additives in pork and pork products.
5. Hazards in the pig breeding establishments.
6. Other relevant factors.

MICROBIAL AND PARASITIC INFECTIONS

These could be divided into two broad categories: (a) zoonoses, i.e. infections of pigs transmitted to man through meat, and (b) contaminants which may enter meat during handling, cutting, processing, storage, etc. and may cause disease in the consumer. For the purpose of this paper, the second category is unimportant as contamination of pigmeat would not differ from contamination of other meats (beef, mutton, poultry) if they are mishandled in a similar manner. Pathogenic bacteria such as *Salmonella, Shigella, Campylobacter,* toxigenic

Escherichia coli, Staphylococci and others can contaminate meats or plant food products (e.g. bread) under unhygienic conditions.

Of the zoonoses, the more important and widespread bacterial infections like salmonellosis, campylobacteriosis and the protozoan infections (toxoplasmosis and sarcocystosis) are not restricted to pigs and may be transmitted from cattle, sheep (and some from poultry) if the meat is consumed raw or undercooked. The infective agents are readily destroyed by proper cooking and salmonellae would not grow in food stored cold or hot even if they are present in small numbers. *Salmonella* and *Campylobacter* ingested in large numbers would produce disease characterised by nausea, vomiting, abdominal cramps and diarrhoea, and sometimes fever. They could cause death in vulnerable groups such as infants, old people and patients suffering from some other diseases.

Of the parasitic zoonoses, the pork tapeworm (*Taenia solium*) infection may result from consumption of raw or insufficiently cooked meat containing cysticerci of this worm. This is generally a subclinical infection and is detected only by faecal examination. The few clinical cases may show nausea, abdominal pains, flatulence, diarrhoea or constipation. In some cases there is debility and weight loss also.

Taeniasis (*T. solium*) is common in countries where pigs have access to human excreta. A similar infection caused by the beef tapeworm (*Taenia saginata*) which is much more widespread than the pork tapeworm,[2] has a parallel life-cycle and a similar pathology. The main danger of the pork tapeworm, however, lies in the fact that its larvae (cysticerci) can infect not only the pig but also man causing a serious disease. If the cysticerci lodge in the subcutaneous tissue or the muscle (even heart muscle) they may not cause any serious symptoms, but often they invade the brain (meninges, cerebral cortex and the ventricles), spinal cord, the eye, and, sometimes several organs simultaneously (disseminated cysticercosis).

Human cysticercosis is a serious problem in countries of Central[3] and South America and represents a heavy burden on the health care services. Most cases of clinical neurocysticercosis treated in hospitals require more than one surgical intervention.[4] Thus, the treatment, which may succeed only in about half of the patients, is cost intensive and difficult.

The larvae of the beef tapeworm (*T. saginata*) do not cause human cysticercosis.

One of the more serious parasitic zoonoses transmitted through pork is trichinellosis. The causal agent *Trichinella spiralis* is a slender worm which lives a few weeks in the small intestine of man and a number of animal species including pigs, dogs, cats, rats, wild carnivores and many others including marine mammals like seals and walruses. The larvae of the worm migrate from the intestine to the muscles of these animals and remain encysted there for years. Human infection results from consumption of insufficiently cooked meat of infected animals or meat products, mostly of porcine origin. The symptoms may start a week or 10 days after ingestion with the start of the muscular invasion phase. They consist of oedema of the upper eyelids, myalgia, headaches, fever, sweating and chills. The disease lasts for 10 to 30 days but muscular pains may persist in some cases for several months. Mortality is generally under 1% but in some outbreaks it may be as high as 30 - 35%.

The pigs get infected through feeding on infected tissues of other pigs, dogs, rats, etc. which may be in the garbage often fed raw to these animals. In recent years, swine trichinellosis (which used to be common in Central and Eastern Europe and in the United States) has been brought under control through boiling of pig feed.

Even so, the infection exists locally in various countries and 50% of pigs in some herds may be infected. In other cases the infection exists in pigs (e.g. in Egypt, where 5 - 10% animals are infected), but human cases do not occur in the local population (Greeks and Copts) as they cook the pork thoroughly. Infections in tourists

who consume undercooked pork have been observed. Wild animals are infected in many parts of the world where human cases are absent or rare.

There are a few other, relatively less common zoonoses which can be transmitted through pork but they are usually only locally important and are transmitted also through other meats and foods. But recent outbreaks in the United States have been traced to pigs more often than to other animals. Examples of such infections are yersiniosis (*Y. enterocolitica*) and listeriosis (*L. monocytogenes*). They are frequently conveyed in milk, milk products, poultry and other meats.

It will be seen from what has been stated above that the two zoonoses which are particularly associated with the consumption of pork are human cysticercosis and trichinellosis. In all other cases various other meats (beef, mutton, poultry, game) are equally or more importantly implicated. Trichinellosis has been cited as the reason[5] and rationale of the prohibition of pork in ancient times.

NON-COMMUNICABLE DISEASES ASCRIBED TO THE CONSUMPTION OF PORK

Anecdotal claims connecting pork as well as other types of meat with various diseases or infirmities abound in different parts of the world. On the other hand, these foods are credited with being cures for disease or having invigorating effects on consumers. Unfortunately, some of these folk beliefs have been uncritically accepted and propagated in "scientific" language by some physicians or other trained persons even in the so-called developed countries. For example, a practising physician recently ascribed[6] the causation of a number of diseases to the consumption of pork. He stipulated the presence in pork of a specific toxin (Sutoxin) and considered cholestrin, histamine, hormones and an oncogenic factor in swine blood to be the causes of various diseases. He thought also that swine influenza virus (dormant in the lungs) may be transmitted to the consumers.

These claims have been critically examined by various scientific bodies and individual scientists and their views have been summarized in the official report of the German Nutrition Association.[7] While admitting that pork may cause food allergy (like other meats, milk, eggs, etc.) they could not substantiate any of the claims and views of Reckeweg and found no evidence of the existence of sutoxin.

Recently, some scientific evidence of the hazards of pork consumption has also emerged. For example, Nanji and French[8] investigated the relationship between average per head consumption of pork, alcohol and mortality from liver cirrhosis in several countries: they found that the correlation between cirrhosis mortality and the product of both alcohol and pork consumption was highly significant. However, in countries and provinces with low alcohol consumption a significant correlation was found between cirrhosis and pork. These observations are important and impressive - but as the authors have remarked themselves this "correlation does not necessarily imply a causal relationship but should be investigated further".

Thus, there is circumstantial evidance of the role of pork in the causation of fatal liver cirrhosis and an accepted role in food allergy. The latter is shared with many other foods of animal origin.

RISK FACTORS IN RELATION TO CHRONIC DEGENERATIVE DISEASES

The two main constituents of meat which are considered to be connected with risk factors of cardiovascular diseases and colon cancer are cholestrol and saturated fats. It will therefore be useful to compare pork with other meats as a source of these constituents.

Cholestrol in human food is derived only from animal products such as meat, milk, eggs and fish. The cholestrol content of some animal products is given[9] in the following table.

TABLE 1: CHOLESTROL CONTENT OF SELECTED FOOD PRODUCTS OF ANIMAL ORIGIN

Product	Cholestrol mg/100 g
1. Beef, lean, trimmed of separable fat	65
2. Pork, lean, trimmed of separable fat	60
3. Chicken, breast meat	79
4. Chicken eggs	504
5. Lamb, lean, trimmed of separable fat	70
6. Veal, lean, trimmed of separable fat	70
7. Halibut (flesh only)	50
8. Liver (beef, calf, pig and lamb)	300
9. Brain	2000
10. Milk	14

It is evident from the above table that pork is not richer in cholestrol in comparison with several other meats and food products. It may be of interest to mention that cholestrol in the muscle (meat) is associated with structures such as cell-membranes, nuclei, mitochondria, sarcoplasmic reticulum etc., but not with visible intramuscular fat (marbling). Therefore the frequent recommendation to avoid fat meat and take only lean meat in order to reduce cholestrol intake has little scientific basis.

Fat is deposited in various parts of the body of animals which consume above maintenance level feeds. In monogastric animals (pigs, poultry) there is a direct relationship of the amount of body fat to energy in the diet which is less apparent in the ruminants. Fat is deposited in two principal sites in the body: Firstly in fat deposits such as the abdomen (peritoneium, around kidneys), around the heart and under the skin (adipose tissue). In some breeds of sheep, there is an additional depot in the tail and in camels in the hump. The second site is the muscle itself which is more limited than the adipose tissue. The chemical composition of intramuscular fat differs in some respects from the fat of adipose tissue which is true fat, i.e. esters of glycerol with fatty acids. Intramuscular fat, like that of other metabolically active tissues has considerable amounts of phospholipids and unsaponifiable constituents.[10]

Fat content of muscle differs in various muscles but also with age and species of the animal, genetic factors, nutrition, hormones, and other factors. For comparison between different species the fat content of Longissiumus dorsi,[11] the longest muscle in the body, is generally used and is shown in Table 2.

TABLE 2: SOME CONSTITUENTS OF THE LONGISSIMUS DORSI MUSCLE FROM MATURE MEAT ANIMALS

Constituent (per cent)	Pig	Ox	Sheep
Water	76.7	76.8	77.0
Intramuscular fat	2.9	3.4	7.9
Total nitrogen	3.7	3.6	3.6

The fat content of Psoas major muscle of pigs and oxen is 1.6 and 1.7% respectively.

For further detailed information on characteristics of meat fats reference is made to Lawrie (1966).[11]

The depot-fat (adipose tissue) can be easily left out of the diet. In fact large quantities of this fat are discarded or used for industrial purposes. It has been said that the depot-fat of pigs (lard) was largely used for making explosives (nitroglycerines) in the two world wars.[12]

Pigs are traditionally considered to be fat animals. This is true for pigs fed on grain and other energy feeds. Most of the pigs outside the industrialized countries feed for themselves generally on rubbish heaps where they act as scavengers. Such pigs have relatively minor fat depots and often have so-called "razor backs" characteristic of debilitated animals. In the industrialized countries also there is an increasing demand for lean and low-fat pork. The breeders have now managed to produce animals with 25 to 40% less fat than was the case two or three decades ago. This has been possible through selective breeding and better understanding of animal nutrition. Such approaches have had much slower results in ruminants, such as, cattle and sheep.

Having compared the cholestrol and fat content of various meats, one could mention briefly their role as risk factors for arterial hypertension, atherosclerosis, coronary heart disease and cancer of the large intestine (carcinogenic faecal steroids).

Relationship between blood pressure and (human) body weight has been established in various epidemiological studies[13,14] on arterial hypertension. However, the causes of obesity are not entirely dietetic as heredity and exercise are also important factors. Nevertheless, animal fat is a rich source of energy and may contribute importantly to increase of weight if other factors are operative. The role of sodium intake in the causation of hypertension is somewhat unclear. Probably relative intake of potassium, calcium or magnesium may be significant. In limited studies, it has been suggested that the adverse effects of high salt intake may be attenuated by a high protein intake.[15] If this is confirmed, meat consumption may have a beneficial effect on hypertension.

Regarding dietary factors related to atherosclerosis and coronary heart disease (CHD), a WHO Expert Committee[16] reached the following conclusions after having examined the available evidence: "Diets in populations having high average total cholestrol levels and mass CHD are characterized by relatively high saturated fat and cholestrol consumption, a relatively high energy intake in relation to energy expenditure (with resultant high relative weight and prevalence of obesity) and relatively low complex carbohydrate consumption." In its dietary guidelines the Committee de-emphasized the consumption of "high-fat meats from domestic breeds as principal protein source" and advised "fish, poultry and lean meats used in small portions". The high fat meats would be the so-called red meats which include beef, mutton and pork.

Epidemiological studies in different parts of the world and experimental studies in animal models have shown that diets particularly high in total fat and low in fibre are generally associated with an increased incidence of large intestine (colon) cancer in man.[17] Furthermore, it has been shown that the diet variables chiefly associated with colon cancer rates are meat and animal protein; total fat, meat and animal proteins are highly correlated.[18] Howell (1975) has pointed out that beef consumption was more related to colon cancer rates than was consumption of pork, poultry or fish.[19]

HAZARDS FROM RESIDUES AND ADDITIVES IN PORK AND ITS PRODUCTS

In countries with intensive animal production various antibacterial agents and growth promoting substances are used to prevent disease and to increase weight and feed efficiency of the meat animal. These substances have important health implications as many of them may persist in meat and viscera of the slaughter animal.[20] The antibacterial agents, such as antibiotics, may cause multi-strain resistance in bacteria

pathogenic for man, e.g. *Salmonella.* This may cause serious problems in therapy when resistant organisms cause human infections.

Among the growth promoting susbstances currently used are natural steroids and xenobiotic anabolic agents like trenbolone acetate, zeranol and synthetic stilbenes.[21] The latter include hexestrol, dienestrol and diethylstilbestrol (DES). The correct use of steroid anabolic hormones poses no known health problems to the consumer. On the other hand stilbene oestrogens are orally active, persist in food and DES is a known carcinogen.[22] Most countries prohibit the use of synthetic stilbenes but illegal use is known to occur.

Antibacterial agents are used in pigs and other meat producing animals but anabolic agents are used much more frequently in calves and poultry than in pigs. In the latter the weight gain is less marked but the proportion of muscle to adipose tissue may be increased.

Of the various additives used in pork products nitrates and nitrites are the most frequent and most important because they are used in the curing process. Also, in industrialized countries the major part of pork is consumed after curing in the form of ham, bacon and sausages of many kinds. Nitrate is readily reduced to nitrite which is used directly also in curing meats. It inhibits the growth of microorganisms (including the highly dangerous *Clostridium botulinum),* imparts a reddish pink colour and a characteristic cured flavour to the meat. In the human body,nitrites are converted into nitrosamines which have been shown to cause hepatic cell tumours in rats. Nitrates are present in virtually all foods, especially in vegetables and in drinking water in some localities. Nitrites are used in curing not only pork but other meats such as beef, turkey meat, etc. It is present in small quantity in the human saliva. Because of the concern about the presence of nitrite residues in meats, efforts are being made to reduce their use in curing and to increase the use of other chemicals, such as, ascorbate and erythorbate which have been found suitable for this purpose. In the meantime the nitrite in cured pork products remains a suspected hazard.

HAZARDS OF PIG BREEDING

People who work in piggeries or handle these animals alive or after slaughter are occupationally exposed to certain infections transmitted through contact or proximity. These are mostly bacterial infections like leptospirosis *(Leptospira pomona* causes swineherds disease), brucellosis *(Brucella suis),* erysipeloid *(Erysipelothrix rhusiopathiae)* and anthrax.Pigs may get involved in the transmission of balantidial dysentery *(Balantidium coli)* which is also transmitted from person to person.

In some areas pigs act as amplifying hosts for Japanese encephalitis virus which is transmitted by mosquitoes. Thus pigs act also as sentinel indicators for the disease before human cases begin to occur.

In comparison to pigs, cattle and sheep can also be reckoned as important sources of human disease. For example, the brucellosis contracted from sheep and goats (Malta fever, *Br. melitensis* infection) is much more serious and more widespread than swine brucellosis. Leptospirosis can also be transmitted from these animals and from cattle.

As stated above, it has been suggested that swine influenza virus dormant in the lungs or lungworms of swine may cause various types of illness in man. This virus is transmissible to man but in recent decades only a few isolated instances of such transmission on a limited scale have been reported. The virus produced acute respiratory illness and the outbreaks were self-limiting. Some bird species, horses and other animals are suspected as sources of epidemic influenza strains, perhaps by recombination among themselves and with human strains. It has also been suggested that strains of human influenza virus may get localized in swine and may be transmitted back to man but this has not so far been observed to happen in nature.

OTHER RELEVANT FACTORS

In the foregoing pages the health effects of biological, chemical and patho-physiological factors related to pork have been considered. In some individuals strong psychological reactions to pigs may be observed. These are enhanced by observation of the scavenging habits of the pigs on village refuse heaps where they eat filth or will wallow in mud mixed with their own excreta. In Australia and Africa south of the Sahara (except Sudan), there were no domesticated pigs before the Europeans introduced them in the eighteenth century. (In Africa wild pigs were present.) Some local communities in these continents took to pig breeding and pork consumption, but many others refused to do so and still avoid this type of meat, mainly because of revulsion (and not religion).

SUMMARY OF THE HEALTH HAZARDS OF PORK CONSUMPTION

The more important and definitely proven hazards connected with the consumption of pork are the two parasitic zoonoses, trichinellosis and systemic cysticercosis. Both these infections can be life threatening and their prevention requires difficult measures including change of food habits.

Of the non-communicable diseases attributable to pork consumption (food) allergy and liver cirrhosis have been shown to occur, though more work is needed to prove its aetiological role in cirrhosis.

Consumption of pork and lard can give rise to hyperlipidaemia, constituting a risk factor in cardiovascular diseases. Furthermore, high pork and lard consumption in a low fiber diet would have a correlation with high incidence of cancer of the colon. However, these risk factors are shared by pork with other meats and foods of animal origin.

Of the additives used in curing pork for preparation of ham, bacon, sausages, etc. nitrites could be a hazard as they are converted to nitrosamines which have been shown to be carcinogenic in animals. The exact risk for man is not known and nitrites are present in many other foods including vegetables and sometimes in drinking water.

Pig breeding establishments can be sources of transmission of zoonoses to people exposed to living animals; these include leptospirosis (swineherds disease), brucellosis, erysipeloid and anthrax. Pigs may also increase chances of spread of balantidial dysentery and Japanese encephalitis. However,other meat animals can also act as sources of some of these zoonoses and of others which may be equally (or more) dangerous.

Pigs can cause strong psychological reactions (e.g. disgust) especially when scavenging on rubbish heaps or wallowing in mud mixed with their own excreta.

ANNEX

Reasons for avoiding pork as food

The Muslims, Jews and some Christian sects reject pork because of prohibitions as revealed in their Holy Books, the Quran and the Bible. God Almighty is all-knowing and our limited knowledge and science cannot as yet understand all the reasons for prohibitions and recommendations contained in the divine guidance and revelations, although we should keep on striving to understand them.

For Muslims, the prohibition of pimgeat was, at first, theoretical as there were no domestic pigs in Hejaz at the time of the revelation of the relevant verses of the Quran, but Islam is a universal religion (din) and was not meant to be limited to any single geographical area. There have been several communities other than Muslims and people of the book *(Kitabis)* who avoid pork. Among the pre-jewish people, the Egyptians of the dynastic period avoided pork some 2000 years before the codification of the Mosaic food traditions. Subsequently, pork consumption re-appeared among certain classes of Egyptians but avoidance appeared once again before the first Persian conquest(525B.C.)[23].In several parts of Ancient Mesopotamia there was an ambiguity with regard to pigs which were considered sacred and unclean at the same time.

Although the Greeks, in general, freely ate pork, there were religious cults in Asia Minor and Crete which avoided this type of meat.[24]

In more recent times, large non-muslim communities in Africa (south of the Sahara), Central Asia (Mongolia), South-East Asia and Oceania also avoid pork;[1] these are mostly pastoral peoples.

Some of the hypotheses which have been advanced to explain the avoidance of pork are as follows:

- Reasons of hygiene and hazards to health.
- The pig is a scavenger and visibly dirty in its habits.
- Pork decays rapidly, especially in warm climates.
- Through eating pork one gains the pig's physical or "personality" characters (This belief is widespread and applies also to many other meats and foods.)
- Human souls transmigrate to various animals including pigs.
- Certain groups have totemic relationship with pigs which may have helped the group in some way in the past, thus becoming sacred.
- Hatred of other human groups which eat pork or at least the desire to remain distinct from them.
- Other reasons including low prestige value, strangeness and psychological feelings of disgust.
- Religious prohibition as illustrated by monotheistic religions has already been mentioned in the first two paragraphs of this section and is a powerful factor in pork avoidance.

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SUMMARY OF DISCUSSION

Dr. Mohd. Ali Al-Bar remarked that when the pig does not exist in the Muslim world then why should we give importance to this problem. On the other hand, scientists mention that pork has some beneficial effect in haemorrhoids. A book written by a Sudanese author mentions that pork is good for heart diseases etc. Regarding contribution of pork to the incidence of cancer; it is said that it could be due to high content of prolactin in the pork. It is however wondered how prolactin present in the pork is going to contribute to the human cancer.

Dr. Khushnood Ahmed Siddiqui commented that to arrive at a definitive conclusion thorough statistical analysis is required for Dr. El-Assouli's research work.

Dr. Amin A. Nanji said that statistical analysis for Muslim countries needs to be done and, for that, data should be collected.

Prof. Abdul Hafiz Helmy remarked that *Balatidinum coli* sometimes causes serious epidemic dysentery which is worse than *E. coli.* In the previous symposium it was thought that Trichinosis would be crept in Muslim countries. And, now in Egypt genuine cases of Trichinosis have been reported.

Dr. Sufian M. El-Assouli said that positive correlation exists between the animal fat and the cancer. However, such correlation does not exist with vegetable oils. Regarding graft rejection, he said even transplantation of liver is well accepted by the recipient animals.

Dr. Mohammed Al-Ashqar enquired if there is no other skin available, can we use the pig skin for grafting. Dr. El-Assouli replied that this question has to be looked into thoroughly by the Islamic scholars.

Dr. Nanji remarked that there are several other factors which contribute for cirrhosis and malnutrition.

CHAPTER IV
(c) ALCOHOL CONSUMPTION: ITS RELATION TO HEALTH

REPORT ON THE THIRD SESSION

The chairman Prof. Dr. Mamdooh Jaber was not present. Prof. Dr. Ekmeleddin Ihsanoglu (Co-Chairman) chaired and Dr. Mohd. Ali Al-Bar moderated the session.

In this session Dr. Amin A. Nanji delivered an invited lecture on "Alcohol and cirrhosis". The other speakers namely Dr. Mohd. Adnan Sakkal and Dr. Ahmed Abu Al-Wafa A. Akhir spoke on "Alcohol and bone diseases" and "Water is the best solvent" respectively. Two scheduled papers by Prof. Dr. Farouk Mohd Ali on "Tyrosine metabolism in alcoholic cirrhosis" and by Prof. Dr. Suleiman Ahmad Suleiman on "Effect of alcohol on development of the brain and activity of brain lysosomal enxymes" were not presented.

At the end of the lectures, the chairman invited the comments, remarks and questions from the audience. Over 150 scholars attended the session.

— Editors

ALCOHOL AND BONE DISEASE

Dr. M. Adnan Sakkal

SYRIA

INTRODUCTION

When Islam prohibited alcoholic drinks, Moslems believed that this habit is a source of destruction of man physically and socially. The lives of many addicts perished slowly and their early death was catastrophic for their family and community as well and even during their life every body was keeping away from them.

The purpose of this paper is to study, as orthopaedic surgeon, the effect of alcohol on human bones, the damaging effect on the structure and component of the bone and the adverse effect on foetus, leaving the other sad human aspect to the others in various specialities.

In the past, it was noticed that alcoholics are exposed to more fracture than non-alcoholics, particularly fractures of femur and upper humerus. It was also noticed that the abuse of alcohol leads to a decrease in the amount of minerals in bones. A survey of records of 107 chronic alcoholics for the number of roentgen diagnostic procedures undertaken during the last few decades showed the following[1]

— the number of roentgen required for an alcoholic patient is 14 whereas the ordinary patient needs 8,

— fractures in the alcoholics are about four times of the normal individuals,

— the number of skull X-ray required for the alcoholic is four times of the normal persons,

— a remarkable increase in the road accidents of the alcoholics with increase in the number of fractures compared with ordinary people,

— gastro-duodenal X-ray and incidents of peptic ulcers are higher in alcoholics than non-alcoholics,

— the number of I.V. urographics and the number of kidney stones diagnosed over the years in alcoholics were not different from non-alcoholics.

The most important conclusion of this study is the higher rate of fractures, and the higher risk of accidents in alcoholics.

This increased risk of fracture in alcoholics is in part due to their increased risk of trauma, but a generalized skeletal disease may also occur in alcoholics. The exact nature and prevalance of alcohol related bone disease is unknown. The pathogenesis is likely to be multifactorial and related to nutritional problems, endocrine and metabolic effects and possible direct effects of alcohol.[2]

The cytogenic damage of bone marrow cells produced by chronic alcohol consumption

A study carried on rats, about the cytogenic effect of alcohol on bone marrow revealed that: pair feeding of rats with nutritionally adequate liquid diets containing 36% of total energy either as ethanol or as additional carbohydrate (in the controls) resulted in blood ethanol concentrations similar to those observed in alcoholics. Alcohol feeding for six weeks increased the frequency of micronuclei in bone marrow erythrocytes, an index of

chromosomal damage in precursor cells. This was associated with bone marrow hypoplasia and erythrocytes macrocytosis, alterations commonly found in alcoholics.[3]

By contrast, acute ethanol administration produced no changes in the bone marrow. Cytogenetic damage of stem cells could lead to alterations persisting after alcohol withdrawal beyond the life span of effector cells.[3]

Bone morphometry in alcoholics

In bone samples from the iliac crest of definite alcoholics, Saville[4] found that the bone ash content of the middle-aged alcoholic man was of the same order of magnitude as that of an old woman. In vivo studies in alcoholics confirmed that the bone mineral content does indeed decrease in this group of patients. In addition, it has been demonstrated that alcoholics have more fractures, particularly of the type related to bone fragility.[4]

The objective of this presentation was to compare some morphometric variables of bone in alcoholics with normative data obtained from individuals without known bone disease. In the Department of Orthopedic Surgery of Malmo General Hospital, a bone biopsy service provides iliac crest bone biopsy with Burkhardt instrument and morphometric evaluation of the bone samples. In a production control study of this activity, it was found that, 38 patients qualified, without doubt, as alcoholics, the osteoclast activity (number of osteoclast per surface bone section), and the osteoid abundance (percentage of trabecular bone surface covered with osteoid) were measured in iliac crest biopsies, from these 38 alcoholic men. In older individuals, the bone mineral content of the forearm decreased so that the reduction in relation to age was comparable to that of women rather than men. Osteoid scans increased in thickness only in alcoholics who had previously undergone gastric resection. Osteoclasts, however, were more abundant in iliac crest biopsies from alcoholics than from non-alcoholic group. Osteoclasts were also more numerous in alcoholics who had undergone gastric resection. Nevertheless, alcoholism causes bone changes, both systemic (possibly hormonal) and local in nature and is characterized by bone resorption.[4]

In another study on radiological changes focused on the region of patella in 40 male chronic alcoholics revealed the presence of erosion in sulcus femoralis which can be developed enough to lead to a restricted movement of the knee joints and radiological changes in the head of femoral bones, similar to a great extent to Aseptic-Necros-Osteoporosis.[5]

It is believed, that these changes are due to the effect of hyperlipoproteinaemia type IV on the patello-femoral joint. These joints show bilateral secondary arthrosis. At the same time as these erosions and defects of the articular surface develop, there are also changes in the femoro-tibial joint.

The effect of alcohol on foetus

A syndrome of the effect of alcohol on the foetus was described and called the foetal alcohol syndrome frequently seen in babies of alcoholic mothers who have 400 ml of wine during pregnancy; the main features of foetal alcohol syndromes are as follows:[6]

1. Pre and post-natal growth failure: infants are short and light for dates at birth and have got poor childhood growth potential.
2. Micro-cephaly, though usually micro-cephalic, normo-cephaly does not exclude the condition in these children.
3. Typical facial appearance:
   a) poorly formed and floppy ears,
   b) short palpebral fissures, small eyes, epicanthic folds. Sometimes squint or unilateral ptosis,

c) maxillary hypo-plasia with prominence of forehead and lower jaw,

d) other abnormalities may include: congenital heart defects, VSD being the common one, dislocation of hips, restriction of movements of some joints, overlapping of some fingers, skin capillary haemoginos and hirsutism.

Estimates that approximately 1 of every 10 persons who consume alcohol is an alcoholic. It is estimated that there are 9 million alcoholics in the United States today; up to 5 millions of whom are female of them the number of child-bearing is estimated to be around 1 million.[7] In a recent study of eight children of those women who fulfilled the 1972 National Council Criteria for Alcoholics, seven children had been admitted to the hospital with delirium tremens. All the children had short eyelid slits and abnormal jaw protrusion while four had vertical folds in the skin on each side of the nose. Five of the eight child subjects had altered palmar crease pattern and joint anomalies that limited movement. Five subjects showed cardiac anomalies, in addition to a delay in the development of mentality and nervous system, observed in all subjects. In another study, 17% prenatal mortality rate reported for children of alcoholic women as compared to 2% for a control group.[7]

Toxicity of ethanol

It has been shown that ethanol (alcohol) rapidly crosses the placental barrier of the fetus and reaches at least the same level in the fetus as that found in the mother (Corrigan, 1976; Jones et al. 1973). Animal studies showed a marked decrease in growth among the embryos treated with 300 ml of ethanol, with a significant overall decrease in total DNA and protein content. Clinical correlation of head size at birth with subsequent brain function have suggested that microcephaly is strongly related to mental retardation. It is estimated that at least one third of the children born of alcoholic mothers, develop foetal alcoholic syndrome and the rest will show variable stage of mental retardation.

Punctuate Epiphyses disease associated with alcoholic foetopathy

The authors report the first three reported cases of children born of mothers with chronic alcoholism and presenting at birth both fetal signs of alcoholism and punctuate epiphyses disease. In these three cases the clinical signs of alcoholic foetopathy were complete. X-rays of the three children demonstrated punctuate epiphyses at the level of the femoral heads, the tarsus and the sacrum. In two cases there were calcifications in the lumbar vertebrae and in one case, punctuate calcification in the trachea. Furthermore, humeral hyperplasia was noted in one of the children. The association of one of the two diseases in these newborn infants led a new physiopathological theory according to which the vitamin K deficiency caused by chronic alcoholism in the mother led in the new born to a minor acquired form of punctuate epiphyses disease.[8]

Changes in bone mass in alcoholics

Acute alcohol intoxication is a frequent finding in patients with fractures. It has been demonstrated that in men with femoral neck fracture the incidence of severe alcoholisms is significantly increased. The samples taken from the iliac crest of these patients demonstrated a decreased bone mineral content and bone mass. The mineral content of the forearm was measured by the method of Gamma-absorbtiometry in addition to measurement of bone mass, in 58 alcoholic patients, and it was found that there is a decrease in bone mass in alcoholics compared to the control group. This deficiency could be enough for fragility seen in alcoholics which predispose them to variable fracture starting with fracture of the neck of the femur. It is believed that this deficiency of bone mass in alcoholics is due to the associated malnutrition, limited movement and liver disfunction.[9]

Osteopenia in alcoholism

The mineral content of the bone was studied by X-ray and spectrophotometry in the alcoholics of various

ages and it was found that there was a decrease in the mineral content of the bone of 3 patients. The difference between alcoholics and non-alcoholics is estimated around 3.3%[10].

THE CONCLUSION

From what is mentioned in this study, we realize that alcohol addition is a slow commitment of suiside by human being; and it is a trgedy for man and society. That is why Islam prohibited drinking, preparing and even looking at alcoholic drinks, with great awareness that alcohol is a devil which corrupts the family, community and the body of man which is created by God in perfection. It is proved that alcohol causes fragility of the bone, decreased minor content and malformation of fetus. It has detrimental effect on the function of liver, predispose to peptic ulcer and badly affects the mentality of the individual.

Apart from the bone, I would like to add here, that, the phosphate deficiency seen in alcoholics damages the muscular tissue as well. The human body needs phosphate to maintain the active function of the cells, to reinforce the Enzyme System, to maintain the acid-base balance and in the production of adenosin tri-phosphate (ATP) which is the source of energy for cell function and without phosphate, cell cannot maintain its energy supply, the metabolism of protein, lipid and carbohydrate is disturbed and consequently all the biological activity is paralysed.[11]

Dr. J. Noshiel, the Deputy Chairman of the Department of Internal Medicine at Health Centre of Texas University - Dallas, Chairman of Medical Service of Veteran Medical Center, says that the presence of alcohol in the body of the alcoholic, initially stumilates the release of phosphate compounds, leading to phosphate deficiency of the muscles in the later stage. This phosphate deficiency in the muscles produces characteristic symptoms and signs which include fatigue, pain in the muscles and bones and sensation of necrosis.[11]

I won't forget my colleague whom I visited one day in Germany at home, and who was suffering from liver cirrhosis due to alcoholism: he was in a very miserable situation. I asked him: (How you feel?) He said: (You ask me how I feel and you know what cirrhosis is. I see death in front of me. I wish I wasn't a physician, knowing how it is, is our problem. I don't know when and how I am going to pass away.) I was looking at his eyes while he was staring at me, as if he wanted to eat me. His hands were trembling when he was trying to show me how large his liver is. I won't forget his drowned voice and his tears and left him but his picture did not leave me for long time. All this indicated, that alcoholic drink is an evil and its prohibition by Islam aims to give the society a person strong in body, soul and mentality. It is the cause of misery, poverty and despair,it is the bacteria of bankruptcy, depression and humiliation.

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TYROSINE METABOLISM IN ALCOHOLIC CIRRHOSIS

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INTRODUCTION

Abnormalities of amino acids metabolism have been reported in humans[1,2,3], dogs[4,5] and rats[6,7,8] ingesting alcohol. These abnormalities are characterized by increased level of aromatic amino acids - tyrosine, phenylalanine and tryptophan as well as methionine and histidine - and depressed levels of the branched amino acids - leucine, valine and isoleucine.

Normally, 98% of the tyrosine is catabolized each day, primarily by intraheptaic enzymes. This involved initially the transamination of the amino acids to 4-hydroxyphenyl pyruvic acid which is then oxidized to homogentisic acid and ultimately to CO_2 (Fig. I).

However, loss of hepatic function due to alcohol intake may increase the contribution of extrahepatic route for the catabolism of these amino acids via their decarboxylation to biogenic amines (tyramine, octopamine, phenethalamine and phenoethanalamine). These amines possess varied pharmacological properties and their chronic accumulation may in part contribute towards the cardiovascular and neurological complications of liver disease.

Alcoholic hypertyrosinemia, demonstrated by us in 1980[9], could be caused by either decreased activity of hepatic tyrosine transaminase or by failure of delivery of tyrosine to the enzyme within the hepatocyte.

Hypertyrosinemia probably resulted from decreased specific activity of tyrosine transaminase in the liver of alcoholics or failure of tyrosine to reach the enzyme within the hepatocytes, depletion of pyridoxal phosphate, the enzyme cofactor or deficiency of ∝-ketoglutarate, the amino group acceptor.

The present study investigates the mechanism of alcoholic tyrosinemia. The strategy employed in elucidating the metabolic abnormalities followed three steps: first; identify the metabolites which have accumulated in the urine or plasma in the basal state, second; stress the pathway with oral load tests using the metabolic intermediates in the pathway, and measure the concentration of the intermediates which accumulate in the urine or plasma. Accumulated metabolites will be proximal to the non-functioning enzyme. These two initial steps will identify the site of the block.

MATERIALS AND METHODS

Subjects:

Eighteen patients with liver cirrhosis and 16 normal subjects (without liver disease). The patients were all homogenous groups, in that all had bled from gastroesophageal varices and were going for elective surgery for decompression of their varices. In addition, their preoperative percutaneous liver biopsies, which confirmed the diagnosis of cirrhosis, showed inactive disease as evidenced by absence of inflammatory infiltrate or new

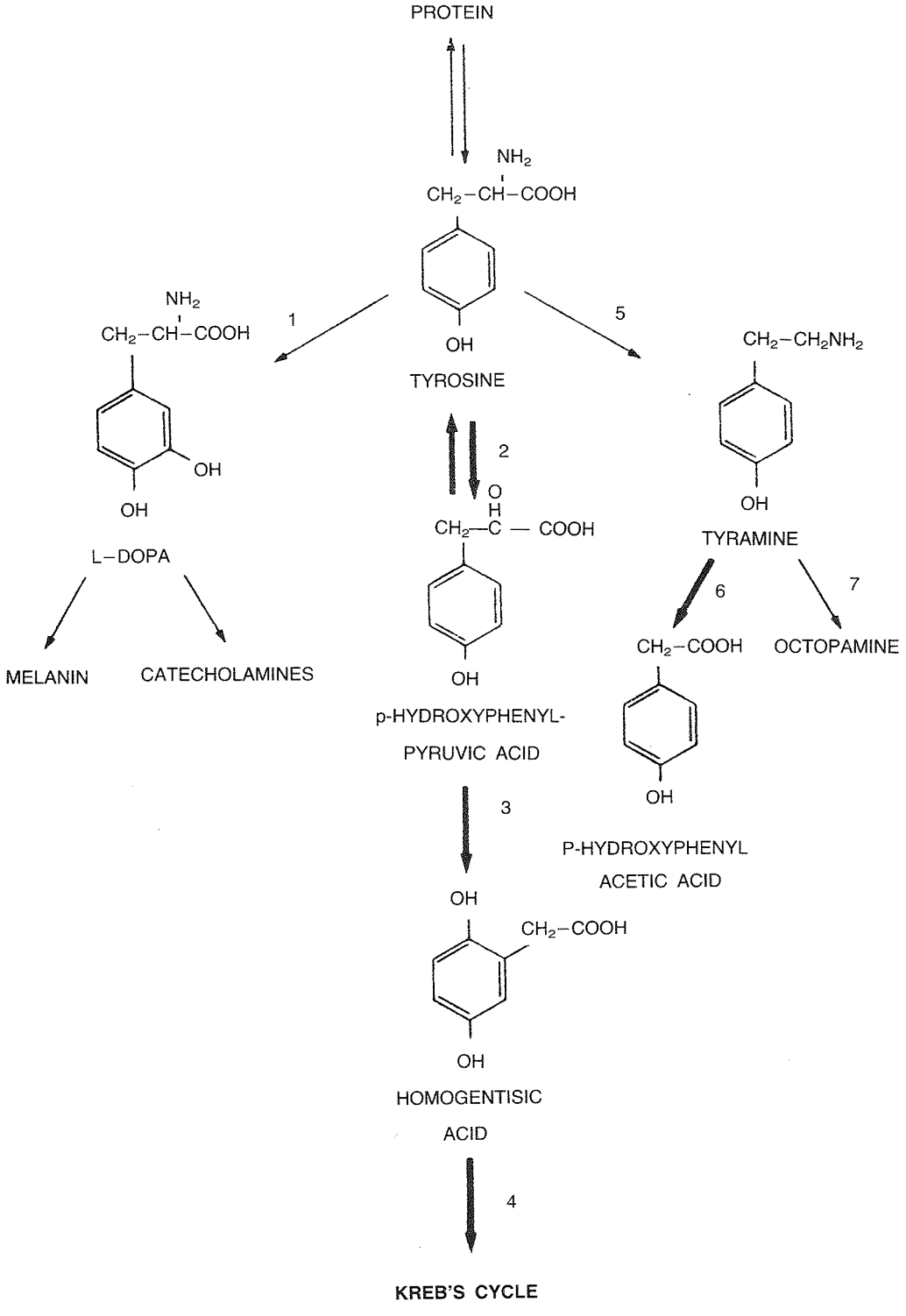
PROTEIN
NH2
CH2–CH–COOH
OH
TYROSINE
1
5
NH2
CH2–CH–COOH
OH
OH
L–DOPA
MELANIN
CATECHOLAMINES
2
O
H
CH2—C — COOH
OH
p-HYDROXYPHENYL-
PYRUVIC ACID
3
OH
CH2–COOH
OH
HOMOGENTISIC
ACID
4
KREB'S CYCLE
CH2–CH2NH2
OH
TYRAMINE
6
7
CH2–COOH
OCTOPAMINE
OH
P-HYDROXYPHENYL
ACETIC ACID

FIG. 1

connective tissue. Table 1 shows, for each alcoholic patient, child's grade (serum albumin, bilirubin, prothrombin time, fasting venous plasma ammonia and degree of portal perfusion as judged on the venous phase of the superior mesenteric artery angiogram.

The 16 patients without liver disease were undergoing elective surgery for a variety of reasons such as peptic ulcer, cholelithiasis, and Hodgkins disease.

Clinical and biochemical liver evaluation:

Each cirrhotic patient received a full liver evaluation prior to commencement of the tyrosine studies, as follows: Serum albumin, bilirubin, and prothrombin time were measured according to standard laboratory techniques[10-12] and Child's classification index was calculated[13]. Fasting plasma ammonia and ammonia tolerance were determined according to an improved method recently developed in this Laboratory.[11] Quantitative tests of hepatic function included galactose elimination capacity[15] and antipyrine clearance[16]. In nine patients, serum ascorbic acid levels were measured because of the role of this vitamin in tyrosine metabolism[17]. Seventeen of the patients had liver angiography, allowing portal perfusion to be graded on the venous phase of the superior mesenteric angiogram[18];grade I represented good portal perfusion and grade IV signified absence or reversal of portal flow.

Tests of tyrosine metabolism:

All subjects were fed with an 80 gm protein diet for 48 hr before the tyrosine metabolism studies, except for patient 1 who ate a 40 gm protein diet because of recent severe encephalopathy. The diet was maintained throughout the study.

The study period covered 7 days. Days 1 and 2 allowed equilibration on the standard diet. Twenty-four hour urine collections were made on each day of the study for PHPA and homogentisic acid measurement. The homogentisic acid load test was performed on day 3. The PHPA load test on day 5, and the tyrosine load test on day 7. Each of these compounds was given as 50 mg/kg body weight in apple juice or apple sauce. Basal fasting levels of plasma tyrosine and tyramine were measured on days 5 and 7. Dietary protein was withheld for 9 hr of the tyrosine tolerance test.

Urine was collected in dark containers over 30 ml glacial acetic acid and refrigerated at −80°C until analysis. Twenty-four hour creatinine content was measured each day to ensure completeness of urine collection. Venous blood (5 ml) was withdrawn at 90 min intervals following tyrosine load for plasma tyrosine measurement.

PHPA and homogentisic acid have a high renal clearance and therefore tolerance to these acids was defined as the percentage of the administered dose excreted in 24 hr in the urine. Tyrosine, on the other hand, in common with most amino acids, has a high renal threshold, and less than 0.5% of the oral dose was excreted in the 24 hr urine. For this reason, tyrosine tolerance was measured in plasma. The methods for calculating tolerances of tyrosine, PHPA and homogentisic acid are given below.

Biochemical methods:

Urinary concentrations of homogentisic acid was measured according to a modified procedure of Lustbert et al[19]. Appropriate dilutions of urine samples were incubated in the presence of $NaNO_2$ (1 ml), 0.1N HCl (0.5 ml), sodium phosphate buffer (2 ml), and diethylene triamine solution (0.8 ml) at room temperature for 30 min. This incubation converted the homogentisic acid to 1, 4 benzoquinone, which formed an adduct in the diethylene triamine. This adduct was measured quantitatively by its absorbance at 385 nm.

PHPA was measured as the enolborate complex according to a modified procedure of Gentz et al (20). Appropriate dilutions of urine were incubated in the presence of 0.8M sodium arsenate (0.9 ml) and 2.0M boric acid –1.0M sodium arsenate (0.4 ml) solution for 2 hr at room temperature. The PHPA complex in the sample was estimated by measuring its absorbance at 308 and 330 A, and the concentration of PHPA was obtained from the following equation:

$$C_{PHPA} = 7.36\ A_{330} - 0.600\ A_{308}$$

Plasma tyrosine was measured by ion-exchange chromatography according to the method of Perry and Hansen[21] and tyramine by radioimmunoassay according to the method of Faraj et al[22].

Calculation of tolerance scores:

Tyrosine tolerance was calculated by plotting plasma tyrosine concentration against time following the oral tyrosine load and, after substracting the fasting tyrosine level, measuring the area under the curve by the trapezoidal rule.

Tolerance scores to PHPA and homogentisic acid loads were expressed as the percentage of the ingested dose excreted in the urine during the next 24 hr. Preliminary experiments demonstrated that excretion of each compound returned to baseline 12 to 18 hr after ingestion of the load.

Statistical analysis:

Degree of association between the various measures of tyrosine metabolism, the clinical liver tests, hepatic encephalopathy, and portal perfusion was determined with Pearson's produce-moment correlation or where appropriate, Spearman's rank-order correlation[23].

Comparison of control patients and cirrhotic patients with regard to various indicators of tyrosine metabolism was analyzed with a two group *t* test or its non-parametric counterpart, the Mann-Whitney *U* test. These two statistical techniques were also used to compare the nonencephalopathic and encephalopathic cirrhotic patients with regard to measures of tyrosine metabolism[23, 24].

RESULTS

The results of the clinical and biochemical liver function tests are shown in Table 1. Our patients exhibited the full spectrum of hepatic damage from minimal to severe. Two parameters deserve further comment. Six of the 18 patients had past or present evidence of encephalopathy, and portal perfusion of some degree was retained in half of the patients. The nine patients who had plasma vitamin C assays all showed results in the normal range.

Basal plasma tyrosine, tyramine, PHPA and homogentisic acid measurements and tolerance scores for the load tests are shown in Table 2. The cirrhotic patients showed significantly elevated levels over normals in basal plasma tyrosine ($p<0.001$), plasma tyramine ($p<0.001$), and basal urinary PHPA ($p<0.005$) but not in basal urinary homogentisic acid. Following the load tests, the cirrhotic patients' tolerance was significantly impaired to tyrosine ($p<0.001$), PHPA ($p<0.05$), and homogentisic acid ($p<0.005$).

When the cirrhotic patients were considered individually, several subgroups could be identified. Of the 18 patients, three showed either an abnormal fasting tyrosine, or an abnormal tyrosine tolerance, whereas the remaining 15 showed elevated levels in both tests. Among these 15 patients, three had normal homogentisic acid and PHPA tolerance, two had normal homogentisic acid but abnormal PHPA tolerance, five had abnormal homogentisic acid but normal PHPA tolerance, and five had abnormal tolerance to both PHPA and homogentisic acid.

TABLE 1: ALCOHOLIC PATIENTS LIVER DATA BASE

Patient	Sex/Age	History of encephalop.	Child's Class.	Albumin mg/dl	Bilirubin mg/dl	Prothrombin time eval.	Ammonia mg/dl	Portal Perfusion	Antipyrine Clearance	Glac. Elim. Cap. (mg/min)
Normals			A	3.5-5.5	0.5-1.3	0	0-50	I	25	360-540
1. G.I.	M.61	Yes	C	3.2	1.74	1.9	88	I	12.0	256
2. J.M.	F.47	No	A	2.9	1.57	2.0	46	I	14.5	228
3. D.S.	M.54	No	B	3.3	1.07	1.3	73	II	15.3	302
4. C.N.	M.52	Yes	B	3.9	1.72	2.4	45	I	29.7	228
5. V.R.	F.48	No	C	3.1	1.72	3.4	30	I	13.6	195
6. D.S.	F.53	No	A	3.6	1.69	3.2	35	III	26.3	340
7. W.S.	M.42	No	B	3.6	1.70	1.7	55	I	14.2	297
8. B.J.	F.44	Yes	C	3.5	1.50	1.6	95	II	14.7	319
9. J.H.	F.46	No	C	2.5	1.28	3.6	150	IV	29.3	256
10. A.M.	M.41	Yes	B	4.0	3.16	1.1	163	III	32.0	351
11. S.M.	M.40	Yes	A	3.4	1.90	1.8	55	III	30.5	325
12. W.W.	M.34	No	C	4.0	1.35	0.9	81	III	14.5	456
13. J.R.	M.55	No	A	3.0	1.40	1.8	46	II	13.5	185
14. J.W.	M.52	No	C	3.0	1.40	1.6	63	II	12.5	274
15. M.W.	F.48	Yes	B	4.1	0.90	4.6	88	IV	14.7	270
16. W.W.	F.69	No	A	2.5	1.00	1.8	88	IV	29.1	230
17. J.G.	M.50	No	B	3.7	2.90	2.9	88	IV	13.6	386
18. R.S.	M.39	Yes	B	3.8	3.70	3.1	78	III	15.6	299

TABLE 2: TYROSINE METABOLISM:COMPARISON OF FASTING TYROSINE (TYR), FASTNG TYRAMINE (T), TYROSINE TOLERANCE AND TYROSINE TRANSAMINASE (TT) OF CONTROL SUBJECTS TO ALCOHOLIC PATIENTS WITH CIRRHOSIS OF THE LIVER (Mean ± S.E.M.)

	No.	Fasting Tyr(nm)	Tyr Tolerance nM/hr	Fasting Tyramine ng/ml	TT Activity Umol/g liver	PHPA (Units/ ng protein hr)
Normals	16	60.7±5.0	499.1±18	1.16±0.12	43±7	0.39±0.12
Alcoholics	18	129.6±85	1235.9±117	2.64±0.17	86±11	1.47±1.0
Significance		P<0.001	P<0.001	P<.001	P<.001	P<0.01

TABLE 3: TYROSINE METABOLISM AND AMMONIA: COMPARISON OF ALCOHOLIC PATIENTS AND NO HEPATIC ENCEPHALOPATHY (HE) VS ALCOHOLIC PATIENTS WITH CIRRHOSIS AND HE (Mean ± S.E.M.)

	Fasting Tyrosine	Tyr tolerance nM/hr	Fasting Tyramine	Basal Urinary HGA (mg/24 hr)
Alcoholics −HE N	105.6±5.1	1082.5±148.3	2.36±0.16	69.0±9.9
Alcoholics +HE	147.6±4.0	1488.8±210.4	3.05±.31	69.8±21.7
Significance	$p<0.01$	$p<0.01$	$p<0.05$	NS

Antipyrine Clearance	Galactose Elimination Capacity (mg/min)
25	360-540
12.0	256
14.5	228
15.3	302
29.7	228
13.6	195
26.3	340
14.2	297
14.7	319
29.3	256
32.0	351
30.5	325
14.5	456
13.5	185
12.5	274
14.7	270
29.1	230
13.6	386
15.6	299

Table 3 shows the results of the tyrosine metabolism tests in the two subgroups of cirrhotic patients, those without encephalopathy (n=12) and those with encephalopathy (n=16). Only the homogentisic acid tolerance score and fasting tyramine differed significantly ($p<0.01$ and $p<0.05$) between these two groups. The mean fasting tyrosine was higher in cirrhotic patients with a history of encephalopathy, but this did not attain statistical significance ($p=0.09$). Patients with past or present encephalopathy showed significantly higher basal ammonia and impaired ammonia tolerance when compared to patients without encephalopathy ($p<0.05$).

Correlation coefficients (Pearson's) were calculated between all parameters measured in both the tyrosine metabolism tests as listed in Table 2 and the general liver data base as listed in Table 1. Several points worth commenting emerge from these correlations. First, tyrosine tolerance score significantly ($p<0.05$) correlated to homogentisic acid tolerance, PHPA tolerance, fasting tyrosine, fasting tyramine and ammonia tolerance. This makes the tyrosine tolerance score the single most useful measure of deranged tyrosine metabolism and also suggests that it detects or correlates with the degree of hepatic impairment demonstrated with the ammonia tests. Second, the homogentisic acid tolerance, fasting tyramine, fasting ammonia, and ammonia tolerance differed significantly ($p<0.05$) between cirrhotic patients with and without encephalopathy. Third, serum albumin, bilirubin, the prophrombin time, Child's classification, galactose elimination capacity, and antipyrine clearance did not differ significantly between these two groups. Finally, there was no significant correlation between tyrosine metabolism parameters and either the tests of liver function or the grade or portal perfusion.

DISCUSSION

Normal and abnormal tyrosine metabolism has been extensively documented in the neonatal period because of the inborn errors which can occur on its degradation pathway. Neonatal tyrosinemia may occur in up to 30% of premature infants and 10% of full-term infants, but it is normally a transient phenomenon[25]. In later life, fasting plasma tyrosine does not appear to alter significantly with age[26] but does become elevated in hyperthyroidism, gross vitamin C deficiency, and hepatic disease[26].

The aim of this study has been to look at the overall picture of tyrosine metabolism in vivo in patients with cirrhosis. Previous reports have shown plasma tyrosine levels, tyrosine tolerance scores[27-30] and basal PHPA levels[31, 32] to be elevated in patients with cirrhosis. The present study confirms these findings with a twofold increase in these indices over normal and extends the findings by building up a complete profile of the homogentisic acid pathway for each patient. This profile shows that nearly every cirrhotic patient (i.e. 15 out of 18) has both fasting tyrosinemia and impaired tyrosine tolerance. Only a minority of these 15 patients excreted abnormally large amounts of PHPA or homogentisic acid in the basal state (three and two individuals). Thus in about two thirds of the cirrhotic patients with impaired tyrosine metabolism, the rate-limiting step in the homogentisic acid pathway appears to be the initial reaction of transamination.

The response of the cirrhotic group as a whole to the PHPA and homogentisic acid levels merits further comment. As has been shown, elevated levels of these metabolites are seen only in a minority, whether in the basal state or after tyrosine load. Nevertheless, eight patients showed an abnormal PHPA tolerance score and 10,an abnormal homogentisic acid tolerance score. Thus, not only are most cirrhotic patients impaired at the transamination step, but about half also exhibit in vivo evidence of impaired PHPA oxidase and homogentisic acid oxidase function. Their failure, in most cases, to excrete excessive PHPA and homogentisic acid in the basal state or after the tyrosine load can be explained on the basis of the tyrosine transaminase defect being the rate-limiting block. The modest degree of PHPA intolerance and homogentisic acid intolerance emphasizes that these are partial blocks in contrast to the total blocks (virtually 100%) found in patients with

the enzymatic inborn errors of aromatic and amino acid metabolism, such as alkaptonuria and phenylketonuria. The homogentisic acid pathways are partial and multiple whereas in the inborn errors, they are total and single.

The absence of a correlation between the measures of tyrosine metabolism and portal perfusion suggests that the defects in transaminating tyrosine and oxidizing PHPA and homogentisic acid are caused by loss in activity of the corresponding enzymes rather than by reduced vascular delivery of the substrates to the enzymes. However, perfusion as judged by the angiographic technique is solely qualitative, and this conclusion must be confirmed by measuring tyrosine transaminase, PHPA oxidase and homogentisic acid oxidase in cirrhotic and normal liver tissue.

Although the hepatic homogentisic acid pathway exhibits the abnormalities described above, alternative extrahepatic degradation routes remain available (Fig. 1). Fasting plasma tyramine in the cirrhotic patients in this series was significantly higher than in controls ($p < 0.001$). Although fasting plasma tyrosine did not correlate with fasting tyramine, there was a significant correlation between tyrosine tolerance score and plasma tyramine. This correlation supports the view that the greater the load put on the impaired principal hepatic pathway, the greater the demand for compensation by minor extrahepatic pathways.

About 90% of the daily degradation of tyrosine normally flows through the hepatic homogentisic acid pathway, and about 1% through the extrahepatic pathway which begins with decarboxylation and leads to tyramine and its derivative actopamine[2]. When tyrosine intake exceeds the capacity of the homogentisic acid pathway in the mouse, as much as 20% of the degradation then proceeds through the extraphepatic decarboxylation pathway[33]. Our data suggest that in hypertyrosinemic cirrhotic patients, an abnormally large proportion of tyrosine is being degraded by the extrahepatic decarboxylative pathway, with resultant elevation of fasting tyramine as we have previously reported[34]. Recent isotopic studies in our laboratory measuring the production rate of tyramine in hypertyraminemic cirrhotic patients have shown that this results from overproduction[35]; the production rate is two to five times greater than normal. The accumulation of plasma and urinary octopamine in cirrhotic patients described by Fisher and Baldessarini[36] presumably results from further metabolism of tyramine along the extrahepatic decarboxylation pathway.

How do these abnormalities correlate with the clinical problem of hepatic encephalopathy? In the present study, the only tyrosine metabolism tests which differed significantly between cirrhotic patients with and without encephalopathy were fasting tyramine and homogentisic acid tolerance score. Homogentisic acid is unlikely to be one of the toxic agents responsible for this condition, since it is so rapidly excreted by the kidneys that none could be detected in the plasma of our patients. Furthermore, congenital alkaptonuria is not associated with mental dysfunction. Although the correlation of encephalopathy with tyraminemia is consistent with the postulated tyramine-octopamine genesis of encephalopathy, the failure to demonstrate a clear correlation with fasting tyrosine and tyrosine tolerance score casts doubt on this hypothesis.

It is probable that hypertyraminemia may have serious consequences. It could result in slow depletion of tissue norepinephrine, because tyramine is an indirect sympathomimetic amine whose action presumably derives from its ability to release norepinephrine. Such an effect could play a part in the hemodynamic and cardiovascular changes sometimes seen in alcoholics. Another consequence of accumulation of tyramine could be increased production of octopamine. Because the usual major route of tyramine metabolism via monoamine oxidase may be blocked in alcoholics by curtailed perfusion of hepatocytes and loss of enzyme, the normally minor pathway tyramine — octopamine could become more predominant.

The relation between plasma tyramine and encephalopathy, however, may be indirect. Tyrosine crosses the blood-brain barrier more readily than tyramine. Thus, in liver failure, tyrosine may accumulate first in plasma and then in the brain. The increased brain tyrosine may then be directed into the synthesis of tyramine

and octopamine. The accumulation of tyramine and octopamine could influence brain function because both the these amines function as false neurotransmitters.

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EFFECT OF ALCOHOL ON DEVELOPMENT OF THE BRAIN AND ACTIVITY OF BRAIN LYSOSOMAL ENZYMES

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INTRODUCTION

Lysosomal enzymes have been shown to be involved in protein degradation in the brain of various animal species[1-3] and humans [4,5]. In addition, lysosomal enzymes may play a role in the regulation of hormonal activities[3,6,7] and in the breakdown of specific proteins which may be involved in disease processes in the brain [5,8].

Ethanol, a very simple molecule, easily penetrates various biological membranes, including the peripheral and central nervous system, causing variety of effects. Among these effects are impairment of neuronal development during prenatal stage[9-12], altered brain development[13,14], physiological and behavioral disorders in the adult and elderly[15,16] . Various studies have been done to understand the biochemical effects of alcohol on the brain and nervous system (for review see 12, 17) but no studies are available on the effect of alcohol on lysosomal enzymes in the brain. The limited studies available deal only with lysosomal fragility[18] with no reference to any developmental stages of the brain.

In the present study, changes in the activity of lysosomal peptidases namely cathepsin B (EC3.4.22.1) and cathepsin D (EC3.4.23.5) during normal development of rat brain including postnatal stage, adult and old age are reported. The effect of alcohol consumption on the activity of these enzymes during the developmental stages of the brain is also reported. The possible relation between the changes in the activity of these enzymes and physiological disorders in the brain is discussed.

MATERIALS AND METHODS

Animals

Sprague-Dawley rats were bred locally. Litters and adult rats of various ages were used in this study. Animals were always sacrificed between 9 and 11 a.m. unless otherwise indicated.

Chemicals

Hemoglobin (type II), 2-napthylamine, benzoyl D, L-arginine-2-napthylamide hydrochloride (BANA), calf thymus DNA, alcohol dehydrogenase and bovine serum albumin were purchased from Sigma Chemical Company. All other chemicals were of reagent quality.

Methods and Assays

All animals were given food *ad libitum.* Alcohol concentration of 15% absolute ethanol (w/v; equivalent to 11.6 v/v) was used in all experiments. In order to test the effect of various doses of alcohol on blood ethanol

content, ethanol was given intraperitoneally (i.p.) to 3 month and 24 month old rats. Blood samples were taken every 30 min from the tip of the tail up to 6 hr. When animals were sacrificed blood samples were taken from the vena cava. Two procedures were used for administering alcohol to postnatal pups. In one set of pups, ethanol was given to their lactating dams in the drinking water. The other procedure involved infusion of alcohol into the stomach of the pups via a catheter on 4-8 postnatal days. In both procedures some of the pups were sacrificed on day 8 and others were sacrificed on day 18 postnatal age. Control pups were given saline solution into the stomach. Some pups were kept till they were 30 days and 60 days old. The pups which were kept to 60 days were re-exposed to alcohol in drinking water at 30 days for two weeks. The controls were allowed to drink water alone. Adults and old animals were given alcohol in drinking water two weeks before they were sacrificed. Pups, dams and all experimental animals were weighed daily during the experiment.

Immediately after animals were sacrificed, blood was collected either from the tip of the tail or from the vena cava. Brains were removed, weighed, placed on ice as a whole or dissected into the three major regions: cortex, cerebellum and brain stem. Whole brains or separate brain regions were homogenized in cooled isotonic saline solution using a Potter-Elvejem homogenizer. The homogenate was then sonicated at high intensity for 1 min using a Fisher Sonic dismembrator and then centrifuged at 25000 x g for 30 min. The resultant clear supernatant was used to assay for lysosomal enzymes.

Cathespin D was assayed according to Barrett and Heath[19]. One unit activity catalyzed the hydrolysis of one μmol hemoglobin per hour of incubation at 37°C. Cathespin B was assayed by the method of Barrett and Kirschke[20]. One unit activity catalyzed the hydrolysis of one μmol of BANA per 10 min of incubation at 37°C. Alcohol concentration in the serum was measured enzymatically according to Buijten and Rydberg[21]. DNA determination in whole brain homogenates was done by an adaptation of the fluorescent method of Williams *et al.* [22], using an Aminco SpF 500 spectrofluorometer with 424 nm excitation and 570 nm emission wave length. The spectrofluorometer was caliberated to read 0 fluroescence unit with a PBS standard and 100 fluroescence units with a 10.8μg/ml calf thymus DNA standard. Protein was determined by the method of Lowry *et al.* [24] with bovine serum albumin as a standard.

RESULTS

In order to determine the effect of various doses of alcohol on the level of alcohol in the blood, four doses were used on two groups of animals (young adults and old rats). As shown in Table 1, the first two doses (1.0 and 2.0 g/kg) resulted in a similar level of alcohol in the blood of both groups. Increasing the dose above 2.0 g/kg resulted in a higher alcohol concentration in the blood of old animals compared to young adults.

Effect of alcohol on developmental changes in brain weight, body weight, protein content and cell number of the brain is shown in Table 2. Brain weight of newborn rats was 0.4± 0.04 g which increased continuously reaching 1.72 ± 0.4 g at two months. The maximum net gain in brain weight was at 10 days (data not shown). Protein content in brain of neonatal rats was 61 ± 5 (mg/g) which also increased continuously reaching 99 ± 8 at two months. Infusing alcohol into the stomach of the 4-day old pups caused a decrease in brain and body weight as well as reduction in brain/body weight ratio at postnatal 18 days (Table 2). Long term effect of alcohol on brain weight of pups was more obvious in females (1.48± 0.08) at the age of 60 days than males (1.56 ± 0.12). Amount of protein was also affected by infusing alcohol into the pups causing a significant lag in protein in both males and females. This lag continued at 30 and 60 days postnatal.

Alcohol treatment of pups also caused a slight decrease (but not significant) in the number of cells in the brain. At the same time there was a slight decrease in the body weight gain with a maximum decrease of 14% at 11 days. At 18 days, the body weight was 8% lower than control and at 30 days it was 7% lower than control. Re-exposure of pups to alcohol at 30 days resulted in maintaining the body weight gain at 8% lower

than control. The brain/body weight ratio was not significant in pups at 18 days but in adults and old animals, this ratio was significantly lower (16%) than the control.

Developmental changes in the activity of cathepsin B and D in whole brain under the effect of alcohol compared to the controls are shown in Figure 1A and B respectively. The specific activity of cathepsin B in the brain of untreated rats followed a certain pattern after birth. It doubled at 4 days then gradually decreased to neonatal level at 7 days. The activity of cathepsin B then sharply increased at 18 days to a peak of 4-fold above neonatal levels. At one month the activity decreased slightly to 3-fold but started to increase again reaching a 9-fold peak at 2 months. Exposure of pups to alcohol at 4-8 days resulted in a slight increase in the activity of cathepsin B at 7 days and 40% increased at 18 days and 30 days. Re-exposure of pups to alcohol at 30 days caused a continuous elevation in the activity compared to the control. Exposure of adult and old animals to alcohol also resulted in 40-50% elevation of specific activity above the control values.

Developmental changes in the activity of cathepsin B in three main regions of the brain and the effect of alcohol on these developmental changes are shown in Table 3. In untreated neonatal rats, various regions of the brain exhibited almost similar specific activity of cathepsin B which remained the same at one week. At 18 days postnatal the activity of cathepsin B increased 3-fold in all brain regions but declined again at 30 days to slightly above neonatal values in the cortex and cerebellum. The least decline was in the brain stem. At two months the activity of the enzyme was elevated again to 3-fold in the cortex and cerebellum and 5-fold in the brain stem.

Exposure of pups to alcohol at 4-8 postnatal days resulted in a significant increase (35%) in the activity of cathepsin B in the cerebellum and brain stem at 18 days postnatal, but no increase in the cortex. In the pups which were kept for one month, activity of cathepsin B remained similar to that at 18 days although the activity in the control animals declined as mentioned above. Re-exposure of pups to alcohol at 30 days maintained the activity of cathepsin B 40-50% above normal values in all brain regions at 2 months. Exposure of adults and old animals to alcohol also resulted in the elevation of the activity 35-40% above control with maximum increase in the cerebellum.

Specific activity of cathepsin D in the whole brain exhibited a biphasic increase during the first 30 days (Fig. 1B). The first peak (2.5-fold) was at 4 days and the second peak (4-fold) was at 18 days. At one month the activity declined to slightly above neonatal values and by two months it was elevated again to 2-fold above neonatal values. Exposure of pups to alcohol at 4-8 days resulted in a slight increase in the activity of cathepsin D at 7 days which became significant at 18 days (40%) and 30 days (30%). Re-exposure of pups to alcohol at 30 days resulted in maintaining the activity of cathepsin D 40% above control at 60 days. Exposure of adult and old rats to alcohol also resulted in elevating the activity of cathepsin D 35% above control values.

Developmental changes in the activity of cathepsin D in brain regions and the effect of alcohol on these changes are shown in Table 4. Similar to the whole brain there were variable biphasic increases in the activity of cathespin D in all brain regions. The first peak was at 18 days and reached 6-fold above neonatal values in the cortex and cerebellum but only 4-fold in the brain stem. The second peak was mainly in the brain stem at two months. Exposure of pups to alcohol resulted in 30-40% increase in the activity of cathepsin D in brain regions with most increase in the cerebellum. Exposure of adults and old rats to alcohol also resulted in elevating the activity of cathepsin D above control values with most increase (40%) in the cerebellum.

DISCUSSION

During postnatal development, most of the gain in brain weight of untreated rats occurs between 5-14 days, with maximum gain at 10 days. Also, the amount of protein increased rapidly during the first two weeks. This is not surprising because the early period of postnatal development is identifiable with considerable

myelination[3] and glial multiplication[24]. Various investigators[25-27] reported that the rate of protein synthesis was highest in brain of young animals and lowest in brain of adult animals. In addition, rats have 'growth spurts' which occur at 2-3 weeks with a peak growth at postnatal 6-9 days[28]. Fluctuation in the activity of cathepsin B and D during the early stages of postnatal development inversely corresponds to these growth spurts. Therefore, by maintaining low activity of proteases and high rate of protein synthesis during postnatal development, this allows for a rapid gain in the weight of the developing brain.

Exposure of pups to alcohol during early stages of postnatal development resulted in a reduction of brain and body weight as well as protein and cell number. On the other hand there was an increase in the activity of cathepsin B and D. The increase in the activity of lysosomal peptidases could play a major role in the reduction of brain weight by increasing protein degradation and decreasing protein synthesis. It was also demonstrated by other investigators[13,14] that infusing alcohol into the stomach of young pups caused reduction of protein synthesis and incorporation of amino acids.

A possible factor for reduction of body weight in pups treated with alcohol could be due to malnutrition and/or ethanol or its metabolite. This effect is more likely to be due to ethanol itself, since it has been reported that alcohol also causes reduction in protein synthesis in the liver and other organs[29,30].

Early postnatal exposure in the present study caused abnormal elevation in the normal pattern of activity of cathepsin B and D. Investigators have reported various metabolic and functional abnormalities as a result of early postnatal exposure to alcohol. Spohr *et al.* [31] reported abnormal development of functional neuronal connections and Goldstein[32] reported abnormality in the synthesis of glycoproteins necessary for cell membranes synaptogenesis function. These abnormalities could be correlated to the changes in the activity of lysosomal peptidases.

Specific activities of cathepsin B and D in brain regions of untreated neonatal rats are uniformly distributed except in the cortex which has lower specific activity. At one week, however, specific activity of these two cathepsins in the cortex matched the activity of other brain regions. This delay in the specific activity of cathepsin B and D could indicate selective changes in the cortex before and immediately after birth (such as synthesis of substance P and myelination). Benuck *et al.*[3] demonstrated a correlation between myelination and activity of cathepsin D. Marks and Lajtha[1] have also shown that activity of cathepsin D is greatly elevated during diseases associated with demyelination. After the age of one month, regional variation in the specific activity of cathepsin B and D are evident with least activity in the cortex. These results are in agreement with the report by Whitaker *et al.*[33] of non-uniform regional distribution of cathepsin D in human brain.

Normal increase in the activity of cathepsin B and D in brain of older animals could be due to an increase in the half life of these enzymes. Dunlop *et al.*[26] have shown that the rate of protein degradation in rat brain diminishes with age and varies in the regions of the brain, being highest in the cerebellum. However, there is no evidence for the presence of inhibitors for these enzymes in the brain at various ages. When supernatants from brain of various ages were mixed, the activity of the enzymes was not affected.

Exposure of adult and old animals to alcohol caused further increases in the activity of cathepsin B and D in brain mainly in the cerebellum and brain stem. Increases of activity in the adult animals was greater than in old ones. This increase could have severe consequences on protein degradation and demyelination in the brain.

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TABLE 1. EFFECT OF VARIOUS DOSES OF ETHANOL ON BLOOD ETHANOL CONTENT IN YOUNG AND OLD RATS.

Blood ethanol concentration (mg/ml)			
Ethanol (g/kg)	Young Adults (3 months)	Old Rats (24 months)	P
1.0	1.25 ± .07	1.59 ± 0.11	NS
2.0	2.13 ± 0.12	2.52 ± 0.13	NS
3.0	2.65 ± 0.11	3.49 ± 0.15	0.001
4.5	3.23 ± 0.17	3.89 ± 0.25	0.05

Animals were killed 30 minutes after the administration of ethanol (15%, i.p.). Values are mean ± S.E.M. of 6 animls in each group.
NS = No significance.

TABLE 2. EFFECT OF ALCOHOL ON BODY AND BRAIN WEIGHTS, PROTEIN CONTENT ON DAY 18 POST-NATAI AGE.

Measurement	Ethanol treated (15)	Control (15)	P
Body weight (g)	34.2 ± 0.92	38.2 ± 1.31	<0.01
Brain weight (g)	1.10 ± 0.07	1.22 ± 0.04	<0.01
Brain/body (ratio)	0.033 ± 0.001	0.032 ± 0.001	0.1
Protein (mg/g brain)	85.7 ± 2.3	96.4 ± 3.5	<0.05
# of cells x 10^9/g brain	1.09 ± 0.02	1.13 ± 0.02	0.1

Values are means ± SEM of 15 animals.
Alcohol was given by gavage for the duration between 4-8 postnatal day and then animals were sacrificed on 18 postnatal day. Assays were done as indicated under methods.

TABLE 3. EFFECT OF ALCOHOL ON REGIONAL DISTRIBUTION OF CATHEPSIN B IN RAT BRAIN AT DIFFERENT AGES

Age of Animal	Brain Region		
	Cortex	Cerebellum	Stem
1 day	1.8±0.17	2.2±0.21	2.3±0.22
	—	—	—
7 day	2.3±0.21[a]	2.7±0.22	2.5±0.24
	3.1±0.32[b]	3.2±0.31	3.0±0.28
18 day	6.2±0.53	7.2±0.61	6.3±0.54
	6.8±0.81	9.8±0.88	8.3±0.73
1 month	2.8±0.22	2.9±0.23	3.2±0.31
	6.2±0.72	8.1±0.73	8.2±0.53
2 month	6.2±0.51	9.1±0.82	14.5±1.12
	8.9±0.87	13.4±1.01	19.9±1.23
6 month	11.6±1.07	16.2±1.12	16.3±1.35
	16.9±1.25	23.4±1.58	21.7±1.74
24 month	10.3±1.02	14.9±1.36	15.4±1.41
	13.3±1.21	19.3±1.48	20.2±1.71

Values are means ± SEM of specific activity (units /mg protein x 10^2) of 6 animals. a, values for untreated animals; b, values for animals treated with alcohol as indicated in the text.

TABLE 4. EFFECT OF ALCOHOL ON REGIONAL DISTRIBUTION OF CATHEPSIN D IN RAT BRAIN AT DIFFERENT AGES.

Age of Animal	Brain Region		
	Cortex	Cerebellum	Stem
1 day	2.1±0.23	3.2±0.29	3.2±0.35
	—	—	—
7 days	3.8±0.31[a]	4.1±0.37	3.8±0.49
	4.9±0.43[b]	5.8±0.49	4.7±0.42
18 days	14.3±1.21	17.4±1.14	12.8±1.36
	19.9±1.17	24.6±1.78	18.3±1.56
1 month	4.2±0.33	3.3±0.21	4.0±0.41
	5.9±0.43	4.4±0.29	5.1±0.43
2 months	6.3±0.42	6.9±0.52	9.9±0.96
	8.2±0.85	9.8±0.79	13.8±1.10
6 months	9.2±0.87	14.9±1.38	15.2±1.36
	13.4±0.98	19.3±1.33	18.2±1.56
24 months	9.7±0.93	15.2±1.53	14.9±1.42
	13.5±1.13	19.8±1.64	18.9±1.88

Values are means ± SEM of specific activity (units/mg protein x 10^2) of 6 animals. ag = values for untreated animals, b = values for animals treated with alcohol as indicated in the text.

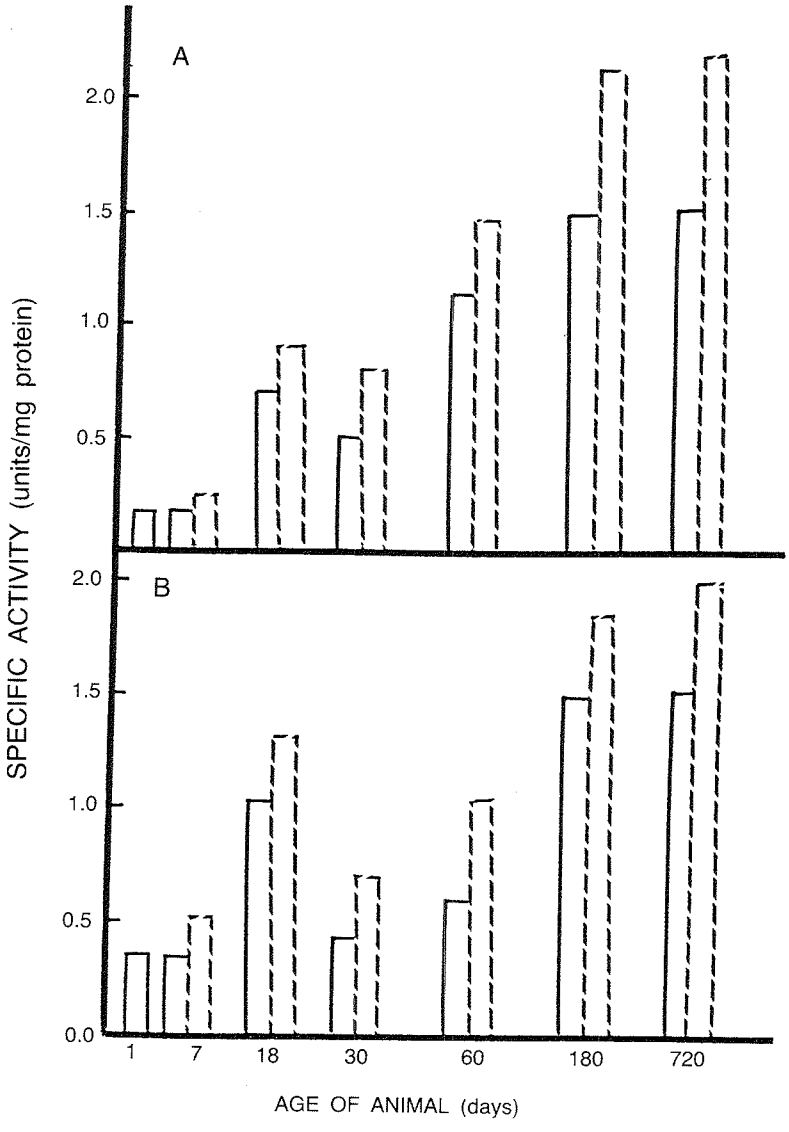

Figure 1. Developmental changes and the effect of alcohol on the activity of lysosomal enzymes in rat brain.

A. Changes in the specific activity of cathepsin B (units/mg protein)

B. Changes in the apecific activity of cathepsin D, (units/mg protein)

Each point is the mean value for 6 determinations.

Histograms with solid lines represent values for untreated animals and histograms with broken lines represent values for animals treated with alcohol.

WATER IS THE BEST SOLVENT

Dr. Ahmed Abu Al-Wafa Abdel Akhir
and
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ABSTRACT

The Almighty "ALLAH" has allowed the taking of all the clean good things and forbidden taking the dirty harmful things. Of the permitted drinkables, water is the most common and best, it is clean in itself and as well it cleans all other stuffs. In direct contradiction to this blessed state of affairs, there is the wine; it is dirty in itself and as such is never capable of cleaning any other stuff. Wine destroys parts of the body by destroying its inner cells. What is said about wine can also be said in regard to alcohols which is the fundamental ingredient of the wine.

Water is the governing factor in the lives of creatures; whether it is the human or other beings. It is the liquid in which all life supporting materials are dissolved and absorbed and detained by the body cells. As such it deserves every attention by the scientists and researchers; more of its qualities and secrets need to be known. Those who are concerned with pharmacological research are particularly involved to embark on studying water as the best solvent. Many should have a firm unshakable belief in this and their researches should be directed to make known this fact to all others. Their goal should be to prove that water can be a solvent to any and every drug or medicine.

We introduce this research — "water is the best solvent" — being guided by our full belief that ALLAH has put in the water all ingredients of satisfaction and man does not need in any degree to revert to the usage of alcohol under all circumstances. Learned religious people have correctly said "God has forbidden wine because He knew when He credited it that it is a disease and not a medicine".

The research is concerned with the properties of water in general and its properties as a solvent. Particular stress was made on factors that may help to make water as the best solvent and menistruom. The research is divided into three parts:

Part I

Water and its properties from an Islamic Point of View: Natural Properties - Chemical Properties, Water and Life.

Part II

Usage of water as a solvent and menistruom. Different pharmacological forms in which water is used. Reasoning why water is preferred over alcohol in drugs.

Part III

Factors that would help make water a better solvent.

Purpose of the research

1. To focus attention on the importance of using water as a solvent.
2. Showing the factors that would improve using water as a solvent and dealing with any problems in this respect.
3. Inviting learned men and researchers amongst pharmacists to pay more attention to water usage.

The research gives useful information and useful studies about the factors that would improve dissolution in water and dealing with the consuming problems. This study may help dispensing with alcohol and using water as a solvent instead, in the drug industry.

As such, this study falls within the scope of the researches concerning the application of Quran and Sunnah relating to the usage of wine and alcoholic drinks which are prohibited by Quran and forbidden by Sunnah either for the treatment or as an encorporant of drugs. Water, the allowed blessed drink is the obvious alternative.

SUMMARY OF DISCUSSION

Dr. Ahmed Shawki Ibrahim enquired whether Quran and Hadith are different from those works which have enamated from research. Alcohol is intoxicant in whatever extent one starts doing research.

Dr. Ahmed El-Kadi remarked that it has been the theme that alcohol was good for heart but it has negative suppressive effect on the myocardial contractility leading to cardiac myopathy.

Dr. Abdullah Badran suggested that there should be a complete ban on alcohol and pork consumption in Muslim countries.

Dr. Sleim Ammar endorsed Dr. Badran's views and advocated for a clear cut recommendation on this account.

Dr. Shoaib Akhtar enquired that since alcohol is a group of drugs, which of this group should be categorized as drinkable?. It is sometimes used in the transfer of "SH" or "O" groups in a compound and sometimes used as a preservative.

Dr. Abu Al-Wafa A. Akhir replied that I mean by ethyl alcohol or methyl alcohol.

One delegate asked whether washing hand with alcohol would spoil Vadu and whether it Haram?

One Sheikh remarked that if alcohol is clean then there is no problem but if it is unclean then ablution will be spoiled. However, there was lot of discussion and finally, he said it can be used for ablution. But Dr. Akhir contended that alcohol is unclean (Najas) and hence it can't be used for ablution. The Sheikh remarked who says alcohol is unclean? Quran says it should be avoided.

CHAPTER V

SOME SELECTED PAPERS - NOT PRESENTED

1. PROHIBITION IN ISLAM
   Dr. K.S. Siddiqi
2. INFECTIOUS DISEASES TRANSMITTED FROM PIGS TO MAN: VIRAL AND BACTERIAL DISEASES
   Dr. Mohammed Ali Al-Bar, *et al*

PROHIBITION IN ISLAM

Dr. K.S. Siddiqi
INDIA

Recent years have witnessed considerable concern about the social menace and health hazards caused by the sedatives. The reckless consumption of tranquillizing drugs has created such a serious problem that remedial measures have so far been proved ineffective. Even the most liberal countries of the world including U.S. and Europe where drug abuse has reached an alarming level are framing legislations to penalise those involved in traffickling of such drugs with a view to save the young generaton from a potentially chaotic situation. The government and scientists are fully convinced that with controlling the use of narcotising chemicals youth power cannot be diverted to constructive activities and whatever the humanity has been able to achieve intellectually and in other walks of life will soon be undone. Ironically, the agnostics who had no faith in Quranic teachings are worst sufferers.

The fact that after ignoring the concept of the Holy Quran and moving in oblivion for too long they have come round the corner is a pointer to the absence of any alternative to the tenets of Islam.

Use of narcotics and liquors is the root of a wide variety of crimes and perversions, the effect of which are brought to bear on innocent teetotaler. The fabric of the society suffers erosion and invites violence. Quran has left no stone unturned in advocating against the use of narcotic sedatives. Prophet Moammad (ﷺ) on innumerable occasions highlighted the adverse implications of these dangerous drugs on the society and public health.

Hadith:

« ما اسكر كثيره فقليله حرام »

English Translation

"Every narcotic or liquor taken even in very little quantity is forbidden (Haram)".

In Sura II *(Baqara)* of Quran, the Almighty advises his creation to keep away from intoxicating liquor or drug and from those who may possibly advocate the beneficial effects of these drugs. He goes a step further to explain that these do more harm than good from the social as well as individual point of view. Thus the English version of the relevant verses is as follows.

THEY ASK THEE CONCERNING WINE AND GAMBLING.
SAY: IN THEM IS GREAT SIN, AND SOME PROFIT, FOR MEN; BUT THE SIN IS GREATER THAN THE PROFIT.
THEY ASK THEE HOW MUCH THEY ARE TO SPEND;
SAY: WHAT IS BEYOND YOUR NEEDS. THUS DOTH GOD MAKE CLEAR TO YOU HIS SIGNS: IN ORDER THAT YE MAY CONSIDER

(S2:V219,220)

Modern researches substantiate this Quranic claim made such a long time back. This strengthens the view that the code of conduct enshrined in Quran is valid for all times to come. The sceptics and those who do

not repose faith in Islam have no reason to limit the validity of Quranic tenets to any particular era or civilization. Several *pseudo notions* are being exposed and myths exploded vis-a-vis the benefits of alcoholic beverages by scientists and doctors. The most popularly held view is that the use of tranquillizer suppresses irritation, helps a person overcome the state of agony and shock and enjoy the pleasures of life without any side effect is just untenable.

Besides alcoholic beverages, opium is another class of narcotics which is more hazardous. It is extracted from poppy. Poppy is an attractive plant of red, purple, white or yellow colour. Opium has a high concentration of alkaloids and when processed it yields a highly addictive substance called heroin. During processing and enrichment of the drug the weight of the raw material is reduced to one tenth. The chemical most prominently used in heroin preparation is acetic anhydride. The 3 countries which find prominent mention in growing and exporting opium and heroin are Burma, Laos and Thailand (Golden Triangle). The derivatives of opium have been coined different trade names and marks some of which are quite popular among the addicts. None of these marketable products is, however, free from ill effects. In raw opium, morphine content is 5-10%. The processed, prepared or cooked opium has 15-20% morphine.

The behaviour and action of addicts following heavy drinking are disliked by God. The person loses balance and gets lost so much that he or she can not concentrate in meditation and goes far away from the spirituality. Under the influence of drug or alcohol the individual shows no regard to cultural and moral values and forgets his due role in the family affairs. In view of these God explicits that alcoholism is satanic trait

(رجس من عمل الشيطن)

and has very emphatically advised against its use. God places narcotising substances alongside excretory and unhygienic matter such as urine and feces so that human beings realize the ill effects of narcotics and alcohol.

(انما يريد الشيطن ان يوقع بينكم العداوة والبغضاء في الخمر والميسر ويصدكم عن ذكر
الله وعن الصلوة فهل انتم منتهون)

God reveals that

Satan introduces enmity, hatred among friends and fellow humans through exploiting the weakness of persons for alcoholism and gambling which turns the human being away from devotion to God.

Harmful effects of alcohol

The alcohol is readily absorbed from stomach and intestine and is transported by blood to various parts of the body. It is basically metabolised in liver, yielding carbondioxide and water as the end products. Heavy doses are thus injurious to the liver where it causes hepatits. There are also reports of the loss of appetite causing constipation and pancreatitis in addicts. Further, the alcohol aggravates peptic ulcers.

The influence on brain may assume very serious proportions. The alcohol is a known depressant of nervous system and interferes with the working of control centers in the brain. This accounts for the abnormal behaviour, uncontrolable desires, loss of etiquettes and violence, etc. Suppression of certain inhibitory centres in the brain leads the person to failure to recognize the social environment and he behaves totally without regard to what the conditions demand. His actions are objectionable, uncomfortable, troublesome to others and below the dignity of man.

BEVERAGES, THEIR SOURCES AND ALCOHOLIC CONTENTS

Beverages	Source	Approximate % alcohol
Bear	Cereals	4 - 8
Wine	Grape juice	10 - 22
Champagne	Grape juice	12 - 13
Cider	Apple juice	8 - 12
Whiskey	Cereals	51 - 59
Brandy	Wine	43 - 57
Rum	Molasses	51 - 59
Gin	Cereals	51 - 69
Rectified Spirit	Cereals	95

Most of the Muslim countries have very stringent laws against trade in the prohibitive drugs and if at all some territory of Islamic world are involved in marketing that is because of the agnostics and foreign nationals. It is heartening to note that even those fundamentalist Muslims who are God-fearing do not consume these drugs despite their involvement in the trade in the killer drugs. However, the fact that Quran prohibits any kind of activity connected with these drugs it is imperative that Islamic ideals are transferred to those ignorant and implemented with utmost sincerity. The ground for such a missionary work is as such fertile and what is required is the efforts of voluntary organizations with dedicated Muslims. The message of Quran against these narcotising drugs and alcohol must be communicated with special mention of the dangers that they may pose to health of consumers and the society as a whole.

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INFECTIOUS DISEASES TRANSMITTED FROM PIGS TO MAN: VIRAL AND BACTERIAL DISEASES

Dr. Mohammed Ali Albar
and
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INTRODUCTION

Allah (Glory to Him) said in the Holy Quran:

HE HATH ONLY FORBIDDEN YOU DEAD MEAT, AND BLOOD, AND THE FLESH OF SWINE.

(S2:V173)

FORBIDDEN TO YOU (FOR FOOD) ARE: DEAD MEAT, BLOOD, THE FLESH OF SWINE.

(S5:V3)

SAY: I FIND NOT IN THE MESSAGE RECEIVED BY ME BY INSPIRATION ANY (MEAT) FORBIDDEN TO BE EATEN BY ONE WHO WISHES TO EAT IT UNLESS IT BE DEAD MEAT, OR BLOOD POURED FORTH, OR THE FLESH OF SWINE, FOR IT IS AN ABOMINATION.

(S6:V145)

He clarified to us the types of food which are forbidden and described them as abomination or filth. He directed people to eat of the good things in the Holy Quran:

O YE PEOPLE! EAT OF WHAT IS ON EARTH, LAWFUL AND GOOD.

(S2:V168)

O YE WHO BELIEVE! EAT OF THE GOOD THINGS.

(S2:V172)

Some Muslim scholars tried to explain part of the divine wisdom for forbidding the flesh of swine and they directed the attention to some infectious diseases transmitted by pigs to man. However, their writings were only limited to two or three parasitic infestations, e.g. *Taenia solium* and *Trichenella spiralis.* In fact, the number of infectious diseases transmitted from pigs to man is rather large. In this paper only the viral and bacterial diseases will be briefly reviewed.

VIRAL DISEASES

The number of viral diseases which are transmitted from pigs to man is rather limited. Some are serious, e.g. Japanese encephalitis while others are less serious e.g. vesicular stomatitis. The pig plays a major role in transmitting some of them where the virus replicates in the pig cells and then are directly transmitted to man. While in others, the first infection is transmitted from the pig to man, then it is propagated from man to man.

An example of such infection is the influenza pandemic of 1918 which resulted in the death of 20 million people. Such pandemics occurred repeatedly since that year till the year 1976, but to a less serious extent.

Arthropods play a role in transmitting some of these diseases, e.g. Japanese encephalitis which is transmitted to man by mosquitoes. In the following account, we will discuss the most important diseases which are transmitted from pigs to man.

1) **Influenza type (A)**

This disease is caused by a member of the family Orthomyxoviridae. It affects man, pigs, horses and birds. There are three major types of the virus and within the types, there are many serotypes, which differ in their nucleic acid. This is consequently reflected in the viral proteins, namely, the hemagglutinin and the enzyme neuraminidase located in the viral envelope. Infection due to one of these serotypes does not give protection the other serotypes. The segmented ribnucleic acid of the virus is responsible for production of new serotypes due to a major change in the base sequence of the nucleic acid called 'antigenic shift' or due to a minor change called 'antigenic drift'. Due to these changes new serotypes emerge every 10-15 years. In 1918, one serotype of swine origin was responsible for a pandemic which killed more than twentyone million people. In 1976, another pandemic due to influenza virus of swine origin occurred but it did not spread as it was expected. The pandemics of 1957 and 1968 were of swine origin. It spread from China which contains the largest number of pigs in the world.

Human types of influenza virus can replicate in pig cells and likewise swine types can replicate in human cells.

2) **Japanese encephalitis**

This disease is common in East Asia. The etiology of the disease is a member of the family Togaviridae which contains yellow fever virus. The virus replicates naturally in wild birds and is transmitted from them to pigs and man by the Culex mosquitoes. The virus replicates in pigs without causing disease in them except death of the fetus and abortion.[4] In man, the virus can cause epidemics, especially in rural areas where pigs are reared. The disease in man may occur without showing clear symptoms or it may cause a severe encephalitis resulting in death. In 1961, an epidemic in Taiwan resulted in the death of 28% of the total cases.[5]

3) **Vesicular stomatitis**

This disease is caused by a member of the family Rhabdoviridae. It affects cattle, horses and pigs. It is transmitted from them to man supposedly by mosquitoes and sand flies. In man the disease is manifested by fever and vesicles appearing in the mouth area.

4) **Foot and mouth disease**

The etiology of this disease is a member of the family Picornaviridae. It affects cattle and pigs. The disease is widely distributed all over the world. It is transmitted from animals to man due to contact with sick animals and their products. In man it causes fever and vesicles in the area of the mouth, hands and feet.

5) **Swine vesicular disease**

This disease is caused by a member of the family Picornaviridae. It resembles Foot and Mouth Disease to a great extent. The infection is transmitted from pigs to man due to contacts with sick animals and their products. The disease in man causes fever and severe pain in joints and muscles.

6) **Encephalomyocarditis**

The etiology of this disease is a member of Picornaviridae. It affects pigs and causes epidemics and

severe disease. It also affects mice and rats causing chronic disease. The disease is transmitted to man due to contacting sick animals and their products causing encephalitis and in rare cases myocarditis.

7) **Ross River fever**

The etiology of this disease is a member of the family Togaviridae. The virus replicates in pigs and other animals without showing marked symptoms. It is transmitted from them to man by mosquitoes of the Genera Culex and Aedes. In man, the disease causes fever, skin erruption and severe arthritis and it occurs in epidemics.

8) **Gastroenteritis in children**

This disease is caused by rotavirus, a member of the family Reoviridae. Different types of the virus cause disease in many newly born animals including pigs where it produces diarrhea. In man the virus causes gastroenteritis in young children.

The human rotavirus was found to grow in pig intestines causing disease. This indicates that swine rotavirus may cause disease in man.

BACTERIAL DISEASES

Pigs play a role in transmitting some bacterial diseases to man and some of them are serious. The most important diseases are the following:

1) **Brucellosis**

This disease mainly affects cattle, goats and pigs. The etiology of this disease are three bacterial species, *Brucella abortus, Brucella melitensis* and *Brucella suis.* The disease affects the pregnant animals and causes death of the fetus and abortion. Transmission of the disease to man may occur due to contacting of the sick animals and their products. The swine bacteria *Brucella suis* is considered the most serious of the three species to man because it is difficult to diagnose the disease in pigs and in man and because there is no effective vaccine for it. Also it causes a serious illness in man manifested by meningoencephalitis, endocarditis, spleenomegaly, cholecystitis, arthritis, nephritis, orchitis and uveitis.

2) **Salmonellosis**

Salmonella species cause many diseases in man and animals. The most important of those are Typhoid, Paratyphoid and food poisoning.

Food poisoning is the most common disease where animals play an important role in transmitting it to man. Pigs and their products, in addition to restaurants' personnel, constitute an important source for the Salmonella which produce the disease in man. Some medical preparations, e.g. digestive enzymes of swine origin may act as a source of infection.[8]

3) **Leptospirosis**

Most of the Leptospira species affect rodents, pigs and dogs. Man is usually affected due to contact of sick animals and their urine. The symptoms of the disease in man are fever and jaundice due to hepatitis. Other organs which are also affected are kidneys, heart and blood vessels causing hemorrhage and hypotension and in rare cases the disease is fatal (Weil's Disease).

The pig plays an important role in transmitting the disease to man through its flesh and other products or by contaminating water sources by its urine which might lead to an epidemic.

4) **Listeriosis**

This is considered as an important bacterial zoonotic disease. The disease is caused by *Listeria*

monocytogenes and pigs play an important role in its transmission to man.[8,9] The most commonly affected are those who are in close contact with pigs. The disease in man may cause death of the fetus and abortion or postnatal death.

5) **Streptococcal infections**

Streptococcus species are widely distributed in man and animals. Pigs play an important role in transmitting them to man. In 1968, streptococcal meningoencephalitis caused a large number of fatalities in man in Holland and Denmark. A similar outbreak of the disease also occurred in the Bengal province in India in 1984 and killed several thousands of people. The source of the infection in the two epidemics was *Streptococcus spp.* of swine origin. Some scientific references recorded that streptococcal meningoencephalitis repeatedly affected pigs. In Britain for example 17 epidemics occurred in 1974, 52 epidemics occurred in 1975 and the figure escalated to 152 epidemics in 1976.

6) **Clostridial infections**

The group of bacteria which cause these infections are anaerobes and they cause a number of diseases in man and animals. The most important species which are transmitted from animals to man are *Clostridium botulinum* and *Clostridium perferingens*, which are responsible for causing food poisoning in man and animals.

It has been found that 30% to 80% of all the carcases of pigs which are slaughtered carry *Clostridium perferingens*. These bacteria are known to be thermostable and were found to survive after cooking.

7) **Anthrax (Malignant pustule)**

The etiology of this disease is *Bacillus anthracis*. It affects cattle, sheep, goats and pigs causing septicemia and sudden death. The infection may be transmitted from animals to man by contacting dead animals or their products such as meat, skin, wool, etc.

There are three forms for the disease in man and these are:

(a) Malignant pustule of the skin and this is the commonest infection.

(b) Malignant pustule of the lungs.

(c) Malignant pustule of the intestines.

8) **Infections caused by *Fusiformis necrophorum***

This bacterium causes a number of infections in pigs, cattle and goats. It is transmitted from animals to man where it enters through the skin and causes an abscess which is accompanied by inflammation of the local lymph nodes. In rare cases the bacteria may enter the blood and reach the lungs or the other internal organs.

9) **Erysipeloid**

This is a professional disease. It affects mainly those who work in close contact with pigs and fish. The bacterium *Erysipelothrix spp.* causes disease in pigs and is also found on the gills of fish. The disease in man causes a redish skin eruption which usually occurs on the hands. The infection is painful and it continues for 2-3 weeks and then disappears. Rarely the bacteria may reach the neighbouring lymph nodes and enter the blood circulation.

In pigs the disease is more severe and may cause skin necrosis, enters the blood and affects the heart and other internal organs.

9) **Infections caused by *Yersinia enterocolitis and Yersinia pseudotuberculosis***

Yersinia enterocolitis is widely distributed in animals mainly pigs, dogs and cattle. Pigs play a major role in transmitting it to man followed by dogs and rarely other animals.

Some epidemics have been recorded in man due to eating contaminated foods, especially chocolates. In children, the disease is characterised by fever, diarrhea which is mixed with blood and pus. In adults, the disease is less severe but in 30% of the cases it is accompanied by arthritis.

Yersinia pseudotuberculosis resembles *Yersinia entercolitis*. However, they can be differenciated from each other by some special laboratory tests. It causes a pseudotuberculosis manifested by inflammation of the mesenteric lymph nodes. Sometimes the infection resembles acute appendicitis and when the laparotomy is performed the surgeon discovers inflammation of the neighbouring lymph nodes, while the appendix is not affected. The infection due to *Yersinia pseudotuberculosis may* cause arthritis and speticemia.

Pig meat is considered the major source of infection to man and the personnel who work in contact with pigs are mainly affected.

11) **Tuberculosis**

Mycobacterium tuberculosis (Humnis) the human type is mainly responsible for producing the disease in man followed by the bovine type *Mycobacterium bovis* and then the avian type *Mycobacterium avium.*

Pigs have been found to suffer from all the three types. The disease is transmitted from sick animals to man due to close contact and affected meat constitutes a source of infection.

12) **Swine dysentery**

This disease is widely distributed among pigs. In Britain for example above 25% of all pigs suffer from the disease especially those reared for fattening where the morbidity reaches 100%.

The disease is caused by a group of bacteria mainly some types of Spirochetes, Fusiformis and *Escherichia coli.* It is characterized by fever and severe diarrhea which is mixed with blood and pus. The disease is transmitted to man by close contact with sick animals or by eating contaminated foods and water.

13) **Melioidosis**

This disease mainly affects pigs, cats, mice, sheep and cattle and is transmitted from sick animals to man. The disease is found in the Phillipines, Sri Lanka, Indonesia, New Ginuea and central Africa.

The infection occurs on the skin and cause a localized inflammation with enlargement of the neighbouring lymph nodes and fever. The infection might spread through the blood to affect the lungs, the brain and other internal organs, causing death if treatment is delayed. The disease may be in the form of acute pneumonia or it may be a chronic condition resembling tuberculosis.

14) **Pasteurollosis**

This disease mainly affects pigs, dogs, cats, mice, birds and cattle. The infection may be transmitted from sick animals to man through close contact. The disease is manifested by pneumonia, septicemia, arthritis and nephritis.

15) **Mycoplasmosis**

The disease in pigs is caused by *Mycoplasma suis* which produce a pneumonia in them. The infection might be transmitted to man especially those who work in close contact with sick animals causing acute pneumonia.

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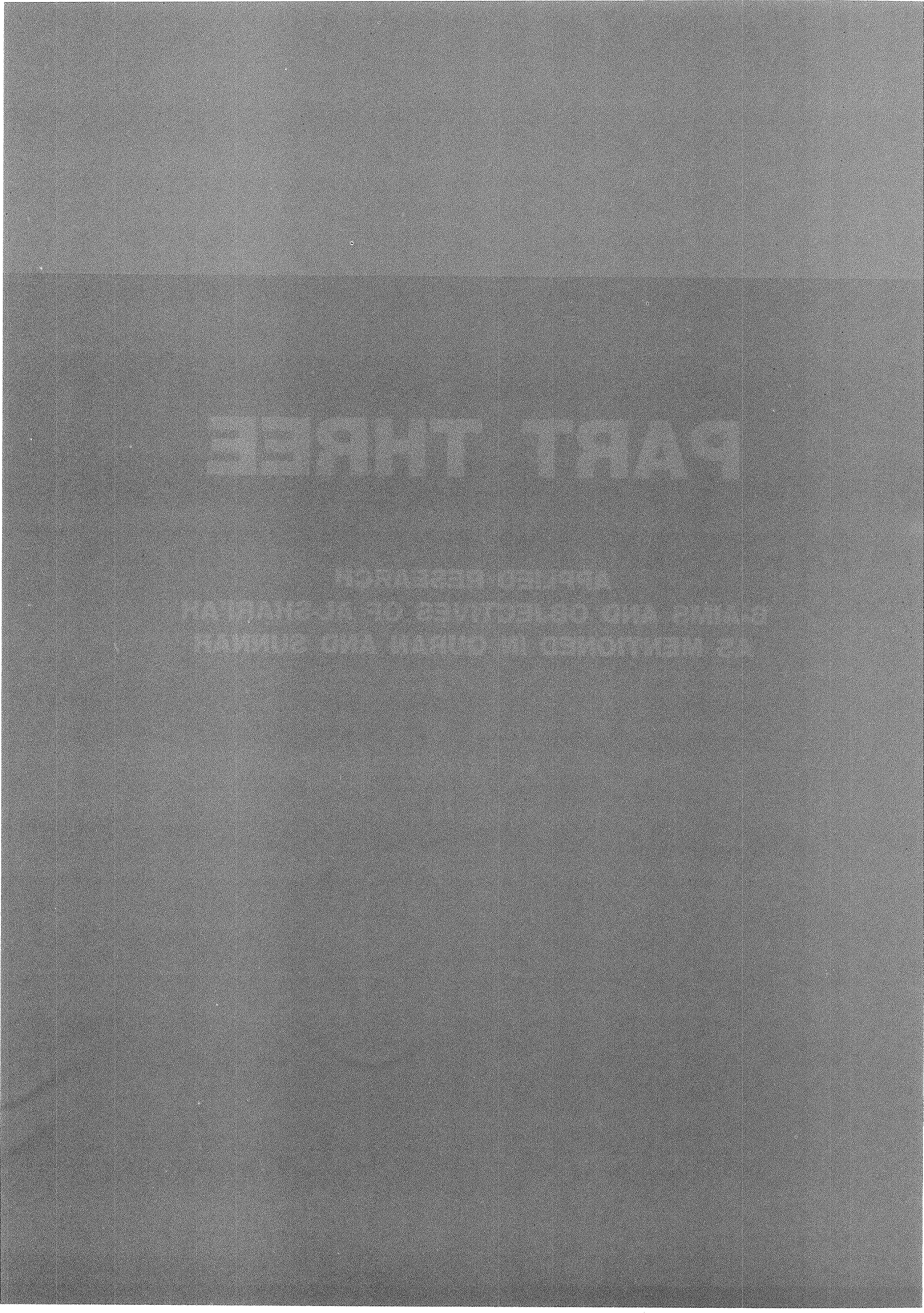
PART THREE

APPLIED RESEARCH
B-AIMS AND OBJECTIVES OF AL-SHARI'AH AS MENTIONED IN QURAN AND SUNNAH



Part Three: *Applied Research:*
B-Aims and Objectives of Al-Shari'ah
as mentioned in Quran and Sunnah.

CHAPTER I

B - AIMS AND OBJECTIVES OF AL-SHARI'AH AS MENTIONED IN QURAN AND SUNNAH

REPORT ON THE FOURTH SESSION

This session was chaired by Prof. Dr. Hussein A. Al-Gezairy and moderated by Prof. Dr. A.H. Helmy Mohammad. The co-chairman Prof. Dr. M.A.H. Qadri was not present.

The speakers in this session were Dr. Ibrahim Mohd. Amer, Prof. Dr. Mostafa Ahmed Shehata, Dr. Adil M. Kandil and Dr.M. Shoaib Akhtar who respectively presented their papers on "Fasting and eye diseases between jurisprudence and medicine", "How nasal wash in ablution keeps body health", "The effect of honey on pathologic liver" and "Chemical composition and effects of honeys of *Apis florea* (small bee), *Apis dorsata* (large bee) and commercial honey on blood glucose levels of normal and hyperglycaemic rabbits".

Over 150 scholars attended the session. At the end of the lectures, the chairman invited comments, remarks and questions from the members of the audience. Many participants took part in discussion, especially on the paper of Dr. Shoaib Akhtar. Some critics sought clarification about the use of honey in diabetes mellitus. Dr. Akhtar offered explanations on his observations in the best possible way.

-Editors

FASTING AND EYE DISEASES BETWEEN JURISPRUDENCE AND MEDICINE

Dr. Ibrahim Mohamed Amer
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This article of research includes the following points :

— Virtue of Fasting.

— The rule of instillation of eye drops and other forms of topical applications to the eye, from both the scholarly and medical points of view.

— Effects of Fasting on some eye diseases.

— There is no occular disease which is deteriorated by fasting.

— The legal rule of Fasting in case of undergoing minor **or** major operations.

It is well known that fasting in the month of Ramadan is the 4th pillar of Islam. It is a duty on the resident, healthy, wise adult Moslem...i.e., one who has no legal excuse such as sickness or travelling for long distances.

The Prophet (ﷺ), said the Qudsy Hadith which is related by Gebril, peace be upon him, who conveyed it from Allah, Who says:

> *"All the actions of Adam's Son are for himself, except Fasting; it is surely for ME and I recompense for it."*
>
> (Extracted by Moslem.)

The Prophet (ﷺ), also said:

> *"Whoever fasts in the month of Ramadan in belief and for the sake (of Allah) is forgiven for all his previous sins."*
>
> (Extracted by Ahmed.)

By reading the above mentioned Hadiths, we can conceive the virtue of Fasting.

THE RULE OF EYE DROPS

In order to give an accurate answer for the conventional question : do instillation of eye drops and other forms of local ocular therapy, spoil Fasting?. To answer such question we will demonstrate both the scholarly and medical views, as follows :

I) Scholarly View :

The scholars define the conditions spoiling Fasting as given below :

— One that reaches the stomach.

— Reaching the stomach via normal inlets e.g. mouth, nose and anus. They do not consider the eye and the skin-bores as normal food inlets.

In the following passages, we may summarise the legal opinions in this respect :

Imam Ibn Hazm said : "as for Fasting, Allah only prohibited eating, drinking, coitus and advertent vomitting. Again, eating or drinking could not be introduced into stomach through eye.

Imam Ibn Taimeah, had given the legal opinion as follows : the legal evidences that prove to spoil Fasting include only what gets access into vein or reaching the stomach.

Sheikh Mahmoud Shaltoot said : "Instillation of eye drops or putting kohle in the eye, do not affect materially Fasting as they are not considered food as such and do not reach the stomach; the place of food and drink".

Sheikh Ibn Baz, mentioned the following Fatwa : "Eye drops do not spoil Fasting, as long as, the eye is not considered as a normal inlet for food".

Sheikh Sayed Sabeq gave his opinion as follows : "Kohle and eye drops or similar medicaments whether one can feel their taste in his throat or not, are numbered among permitted conditions during Fasting, because the eye is not used as an inlet to the stomach". Also, he mentioned that Annas Ibn Malek had put kohle in his eyes while he had been Fasting. Again, Al-Shafae's followers, Abu Haneefa, Ibn Omar and other scholars, accepted the above mentioned legal rule.

II) Medical View :

When a patient puts one drop in his eye, as prescribed by the ophthalmologist, we observe that a fraction of it falls down out of the eye. The greater part of the remainder fractions is absorbed by the ocular tissues particularly the conjunctiva and the cornea; whereas the lesser part which, in fact, is very small in quantity blend with tears. The latter is drained via the lacrymal drainage system, beginning from the lacrymal punctum and ending with nasolacrymal duct in the lateral wall of the nasal cavity.

At this point, this lesser part reaches the nasal cavity and a fraction of it may be discharged outside with nasal secretion on blowing up the nose. The remainder fraction, which is negligible, is directed towards the nasopharynx by the action of nasal cilia, which work posteriorly and regularly pushing secretions from the nasal cavity into the nasopharynx. This explains, to us, why a person feels the taste of some eye drops which may have bitter taste in his throat due to stimulation of taste buds present in the soft palate & posterior 1/3 of the tongue. Such eye drops as chloramphenicol eye drops whether alone or with other drops in combination. Truely, this is only the taste of eye drops itself and does not affect Fasting by any way.

From the above mentioned passages, we find that, both the legal and medical views agree with each other. Also, it is accepted that, other topical applications e.g. eye ointments **or** conjunctival injections which are used for treating eye diseases, are submitted to the same legal rule as eye drops.

On the other hand, it is mandatory to use eye drops and other forms of topical applications during Fasting for treating various groups of eye diseases, for example, glaucoma, ocular inflamations (whether viral, bacterial, fungal or parasitic in origin), allergic conditions, dry eye as well as post-operative medication.

EFFECT OF FASTING ON EYE DISEASES

It is worth mentioning that, some eye diseases improve markedly with Fasting. Allah, Blessed and Exalted be He, made Fasting, beneficial to man's health. We may conceive this meaning from Quran, as Allah says :

AND IT IS BETTER FOR YOU THAT YOU FAST, IF YOU ONLY KNEW

(S2:V184)

We may give an idea, in brief, about the most important eye diseases which improve with Fasting, as follows :

Primary Glaucoma

A) Chronic Simple Glaucoma :

It is known that this disease occurs, in the 6th decade of life and affects males and females with the same ratio. This disease is characterised by an increase in intra-ocular tension, visual field changes and optic cupping and eventually leads to optic nerve atrophy.

In this research work, a certain group of patients of glaucoma were submitted to weekly measurement of I.O.P. i.e. tonometry, one month before Ramadan, during Ramadan and one month after Ramadan. The study revealed reasonable lowering of (7-10 mm Hg) of ocular pressure during Fasting.

It is an established fact that, this disease was found to improve markedly with Fasting especially if the patient Fasts both duty and sunna Fasting. We may explain this improvement by the following mechanism : during Fasting, haemoconcentration occurs and this in turn, leads to diminished secretion of various glands in the body, including the ciliary body processes which secrete the aqueous. So the rate of formation of the aqueous diminished, resulting in lowering the intra-ocular pressure (I.O.P.). Really, this is the same mechanism which is produced by the use of drugs diminishing I.O.P., by inhibiting the activity of ciliary body processes, such as Diamox.

B) Acute Congestive Glaucoma :

Acute congestive glaucoma may occur in the 5th decade of life and affects females more than males with ratio 3 : 1. The irritable, nervous and emotionally disturbed persons are more liable to this type of glaucoma. Again, hypermetropic persons with small eyes and shallow anterior chamber are also susceptible to acute congestive glaucoma.

During Fasting, Moslem usually enjoys good psychological state, spiritual clearance as well as cardiac reassurance. Such conditions lead to established psychic and nervous state of the Fasting man. So, he is less liable to psychic and nervous disturbances, which in some circumstances, may predispose to an attack of congestive glaucoma. It is worth mentioning that, the role of Fasting in such cases, is considered principally preventive.

Retinopathies

Some systemic diseases, may lead to certain types of retinopathies. Such retinopathies are mentioned vide infra :

— Hypertensive retinopathies.

— Arteriosclerotic retinopathies.

— Diabetic retinopathies.

The role of Fasting in these cases is essentially preventive. We may explain this point that Fasting ameliorates cases of hypertension, arteriosclerosis and diabetes mellitus. This results in breaking chain of pathological changes which may lead to occurrence of these retinopathies.

In well established retinopathies, Fasting prevents deterioration and further complications associated with such retinopathies.

It is worth pointing that, there is no ocular disease that deteriorates by Fasting, as long as the patient uses the medicaments prescribed by the ophthalmologist, including the topical applications e.g. drops, ointments etc. As we concluded vide supra that, all topical applications to the eye, do not spoil Fasting.

FASTING AND EYE SURGERY

Surgical operations of the eye may be minor or major. The role of Fasting in both minor or major eye operations, may be demonstrated as follows :

A) Minor Operations :

Minor eye operations such as those for trichiasis, chalazion, post-trachomatous degenerations (p.t.ds), pterygeum, removal of superficial foreign body.... etc do not affect Fasting by any way. Patients who undergo any major eye operations can fast as Fasting does not cause any harm to them by any form.

In this respect, we may extract the verse that copes obviously with this meaning. Allah,the theAlmighty says

... AND IT IS BETTER FOR YOU, THAT YOU FAST, IF YOU ONLY KNEW

(S2:V184)

If the patient needs any systemic treatment e.g. antibiotics; the ophthalmologist can prescribe either injections or long acting antibiotics by mouth, to be ingested, along the period lasting between sunset and dawn. On the other hand scholars gave legal opinion *(Fatwa)* that all injections except glucose, do not spoil Fasting.

B) Major Operations :

A patient who undergoes major eye operation such as cataract, glaucoma, Keratoplasty, retinal detachment operation...etc is exempted from Fasting. This, of course, indicates the ease and tolerance of Islam.

The sayings of Allah, Blessed and Exalted be He

ALLAH DOES WISH TO LIGHTEN (YOUR DIFFICULTIES) : FOR MAN WAS CREATED WEAK...

(S4:V28)

AND

ALLAH INTENDS EVERY FACILITY FOR YOU; HE DOES NOT WANT TO PUT YOU TO DIFFICULTIES..

(S2:V185)

Also He says

AND (ALLAH) HAS IMPOSED NO DIFFICULTIES ON YOU IN RELIGION ...

(S22:V78)

Such verses emphasize the meaning of the ease and tolerance of Islam.

Moreover, some Hadiths, said by the Prophet (ﷺ), also confirm this meaning. Such Hadiths may be given as follows: The Prophet (ﷺ), said

"No harm inflicted or received" Also, He (ﷺ) said *"This religion is easy. No one will ever challenge religion but religion will vanquish him"(Extracted by Al-Bokhary.)*

It is worth mentioning that, the patient should fast later after the period of convalescence following the operation as long as he is healthy. We may conclude this from the saying of Allah the Almighty

..BUT IF ANY ONE IS ILL, OR ON A JOURNEY, THE PRESCRIBED PERIOD (SHOULD BE MADE UP) BY DAYS LATER..

(S2:V185)

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HOW NASAL WASH IN ABLUTION KEEPS BODY HEALTH

Dr. Mostafa Ahmed Shehata, Dr. Awatef Awwad
and Dr. Mohammed Selim
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The nose at the top of the respiratory tract is peculiar as an organ exposed constantly to the drying, cooling and infecting effects of respiratory air passing over its surface at high velocity. By its vibrissae, mucosa and mucous secretion it works actively in filtration of air bacteria, that accumulate in the nasal vestibule in large amounts and of variable types.[1] Full of bacteria, the nose acts as a focus for transmission of this bacteria inside the body and also to the skin and the atmospheric air. By depressing the amount of nasal bacteria by any local measure, a rapid reduction of both skin and aerial bacteria, can be obtained[2], as most of bacteria, especially *Staphylococcus aureus* on the skin, clothes or even in air are coming from the individual's own nose.[3] Hence we can say that the heavy contamination of the nose by pathogenic bacteria is responsible for the spread of many inflammatory diseases as sinusitis, otitis media, laryngitis and respiratory infections beside inflammations of the urinary tract, and skin wounds.[4] This can explain the low incidence of post-operative sepsis (2%) in persons who are not nasal carriers of pathogenic organisms, while it is high (7%) in chronic bacterial nasal carriers. They may even convey their pathogenic bacteria to other people with resultant sepsis.[5]

The risk of nasal staphylococcal cross infection and also other pathogenic organisms can be eliminated by variety of local antiseptic measures as the use of protective masks, nasal douching and cleaning by antiseptic solutions. Perhaps the simplest and easiest method for proper nasal hygiene is the frequent washing of the nose by clean water through deep inhalation of water then sniffing it out.

Islam, the last heavenly religion, conveyed by Prophet Mohammad (ﷺ) takes much care about personal cleanliness and general body health. So it advised its followers to care about nasal cleaning, five times every day, by inhalation of water, and its strong sniffing during the process of ablution that precedes daily praying. In this respect there are many sayings narrated by the pupils of the Prophet (ﷺ) that shows the importance and ways of nasal washing at ablution.

The process of ablution itself was further explained in other sayings, where the Prophet (ﷺ) advised washing the hands three times before their use for nasal inhalation,

> *"on the start of ablution, one should take water in hands to be washed three successive times.*[6]

The way and number of nasal inhalations were well explained in another saying

> *"One should inhale water strongly to the nose at ablution except if he is fasting",*[6] *"You must inhale water two or three times strongly at ablution".*[7]

BACTERIA OF THE NOSE

Due to its function of trapping air bacteria and filtration of respiratory air, the nose is actually a large

reservoir of bacteria. These bacteria are of many groups and species, that vary in density and type according to person, place, season and environment. The following is the usual way of their classification:

1. Coagulase-positive cocci as *Staphylococcus aureus.*
2. Coagulase-negative cocci as *Micrococcus, Pneumococcus, Streptococcus* and *Sarcinia* species.
3. Diphtheroids that may be lipophilic or non-lipophylic.
4. Enterobacteria as *Klebsiella pneumoniae, Enterobacter aerogenosa, Proteus mirabilis* and *Escherichia coli.*
5. Rare forms as Gram-negative cocci.[8]

Bacteria living on the skin of the body or that of the nasal vestibule are accumulated on the outer keratinised layers of the epidermis.[9] It follows that bathing with clean water or washing with dilute antiseptic solutions can remove many of these bacteria. This was well demonstrated in the experiments of Price in 1938, who used a technique of repetitive scrubbing with water, to enumerate bacteria on selected surfaces of hands and forearms, and was able to conclude optimum time needed for complete sterilization of skin.[10] Davis and Noble in 1963 did nearly similar researches, with the same results.[11,12] This was also studied by Scheerman et al. (1960) , and Speers et al.(1965) who found that skin washing reduced surface bacteria markedly, but it returned to its usual condition within 24 hours after washing.[13,14]

The density and variability of nasal flora in man is usually influenced by personal habits, traditions, race, age and the use of general or local antibiotics. All these factors have their important role in the variability of types and species of nasal bacteria.[15,16,17,18,19]

NASAL DEFENCE MECHANISM

The skin of the nasal vestibule which is usually heavily contaminated by bacteria has a good defence mechanism. The sebaceous secretion has a disinfectant property by its free fatty acids that exert some antibacterial activity.[20] The nasal vibrissae entangle bacteria carried on dust particles, that are then expelled to the outside. The nasal mucosa is richly supplied with goblet cells and mucous glands, that help to cover the nasal mucosa with a thin film of mucous secretion. This mucous secretion has a bactericidal function by virtue of its lysozyme content, but unfortunately the common pathogenic cocci are not sensitive to it.[21,22] The cilia of the nasal mucosa has also their role in this protective mechanism, as they move constantly in a backward direction, to expell all the collected dust particles and bacteria.[21,22,23] (Fig. 1)

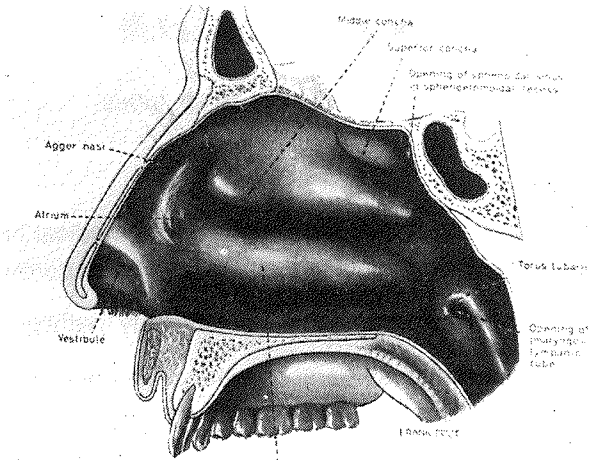

Fig. 1: Anatomy of the nasal cavity.

MATERIAL OF STUDY

To verify the effects of frequent daily nasal washings in the process of ablution, among regular moslem prayer performers a clinico-bacteriological study on normal healthy nose of a large group of persons was conducted, during two years period (1983 and 1984) in the Alexandria Faculty of Medicine. Two hundred medical students, with normal healthy nose were selected at random for this study. They were of both sexes and nearly the same age. One hundred of them were regular performers of prayers, who used to wash their nose frequently at ablution, while the other hundred were non-prayer performers who rarely wash their nose. The first group was the basis for this study, while the second was the comparative control group. This way of selection of nearly similar persons in age, profession, place of living and environment conditions put the whole studied cases under the same conditions and assure an accurate research work.

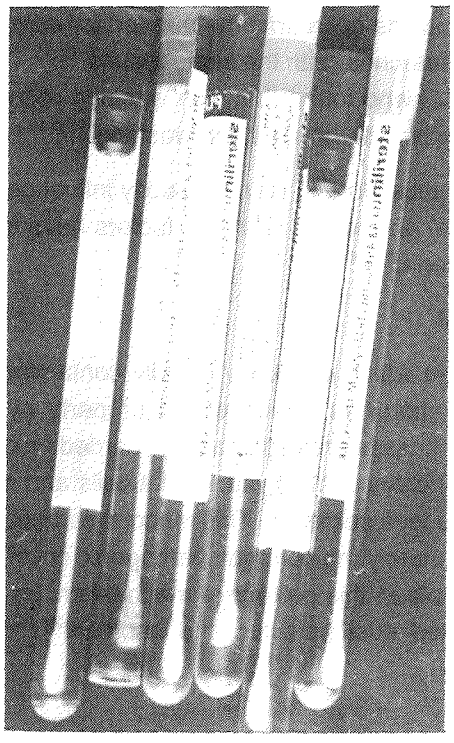

Fig. 2: Sterile disposable swab tubes.

METHODS

All the studied cases were subjected to a full detailed personal and medical history, beside an inquiry about the way and frequency of ablution, in the regular moslem prayer performers (Fig. 2, 3, 4, 5, 6).

A clinical nasal examination was always performed to exclude any pathological cases.

On their first visit to the research department, all persons were bacteriologically examined, by a nasal swab using sterile disposable tubes. These swabs were taken only once from the non-prayer performers, but six times from the prayer performers. The first swab before ablution, the second after nasal ablution without hand washings, the third after a full careful ablution, the other swabs were taken at hourly intervals after ablution.

Fig. 3: Procedure of intake of nasal swab.

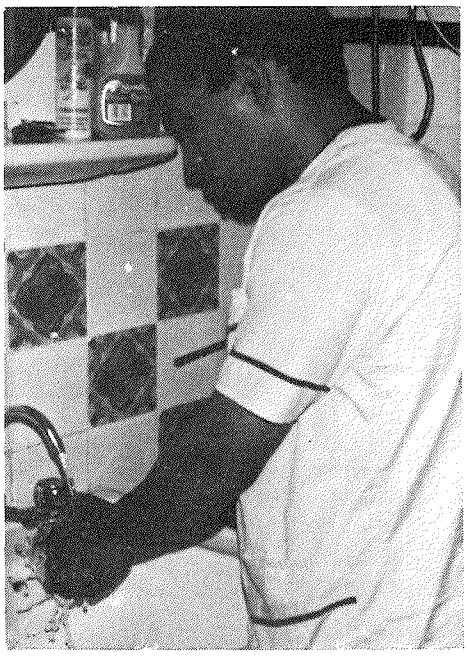

Fig. 4: Hand washing at the start of ablution.

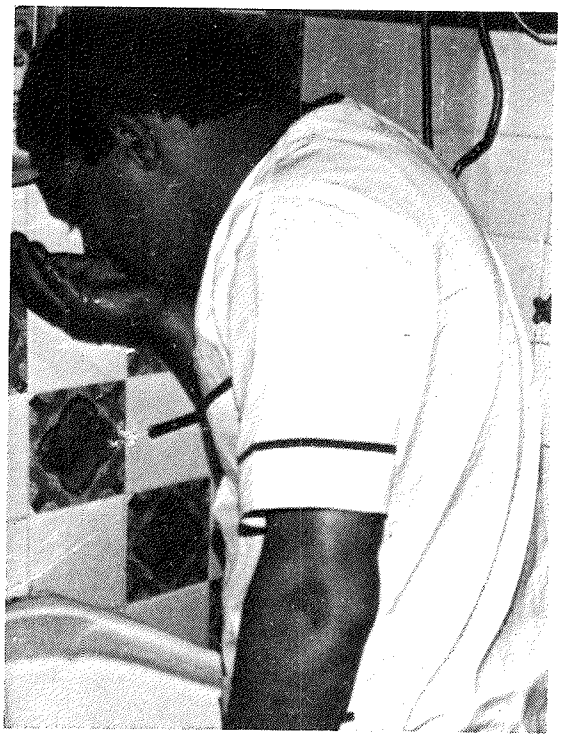

Fig. 5: Water inhalation to the nose, as done in ablution.

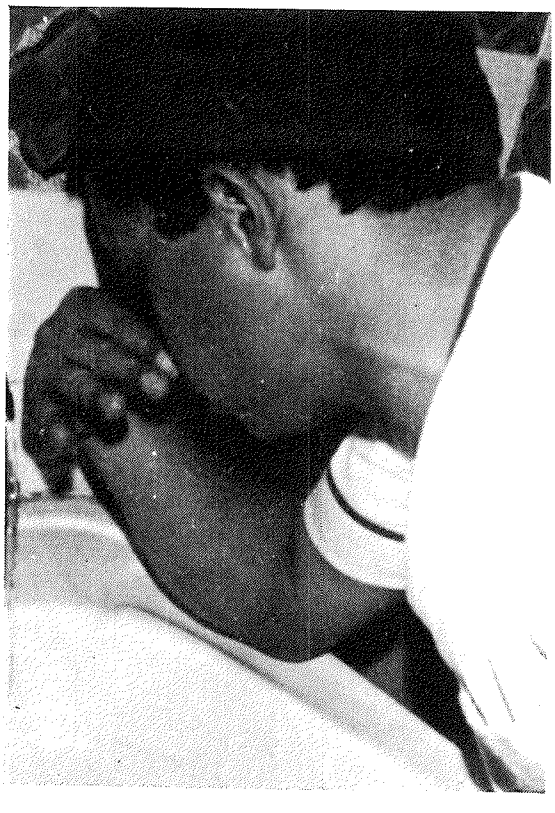

Fig. 6: Water sniffing as done in ablution.

RESULTS

Clinical examination of the prayer performers nose (100 persons) showed healthy nasal vestibule and cavity. Their nasal vibrissae were usually thick, clean, stout and lustrous beside their firm attachment to the nasal vestibule. The nasal tip was usually shining and the nasal alae non-greasy. The nasal vestibule and cavity showed scarcely any debris or crusts. On the other hand, the nose of non-prayer performers (100 persons) showed dirty greyish vibrissae that were usually dull, lusterless and occasionally falling on swabbing. The nasal tip and sides were usually dim and covered with oily sebaceous secretion. The nasal vestibule and cavity showed occasional fine crusts and dust particles (Table I).

TABLE I: CLINICAL PICTURE OF THE NOSE IN PRAYER AND NON-PRAYER PERFORMERS.

Clinical Characters	Percentage of prayer performers	Percentage of non-prayer performers
Nasal tip clean and lustrous	82	16
Sides of the nose non-greasy	84	40
Nasal vibrissae clean	64	28
Lustrous	92	48
Loose	4	44
Presence of intranasal crusts	18	54

Bacteriological examination of the taken swabs from the prayer performers at the different periods mentioned before and from the non-prayer performers gave valuable results that were of great significance.

Those taken from the non-prayer performers revealed the presence of high incidence of variable organisms that were present in large densities and good amounts, in nearly all the studied cases. If mentioned according to their frequency and amount, we got the Staphylococci in 94% (*Staph.aureus* in 64% and *Staph. albus* in 30%), the Streptococci in 22%,(*Strept. viridans* 14%,*Strept. pneumonia* 6% and *Strept.pyogenes* in 2%), the *Diphtheroid bacilli* in 20%, the *Klebsiella pneumonia* in 12%, the *Escherichia coli* in 2% and *Neisseria saprophytic* in 2%, the *Proteus vulgaris* in 2%. Sterile swabs were obtained in 4% of the studied persons (Table II) (Fig. 7).

TABLE II: BACTERIAL TYPES OF THE NOSE IN ALL PERSONS BEFORE ANY NASAL WASHING.

Nose Bacterial Contamination	Prayer performers percent	Non-prayer performers percent
Staphylococcus aureus	42	64
Staphylococcus albus	26	30
Streptococcus viridans	12	14
Streptococcus pneumonia	2	6
Streptococcus pyogenes	0	2
Diphtheroids bacilli	12	20
Klebsiella poneumonia	4	12
Neisseria saprophytic	0	2
Escherichia coli	0	2
Proteus vulgaris	0	2
Sterile cases	20	4

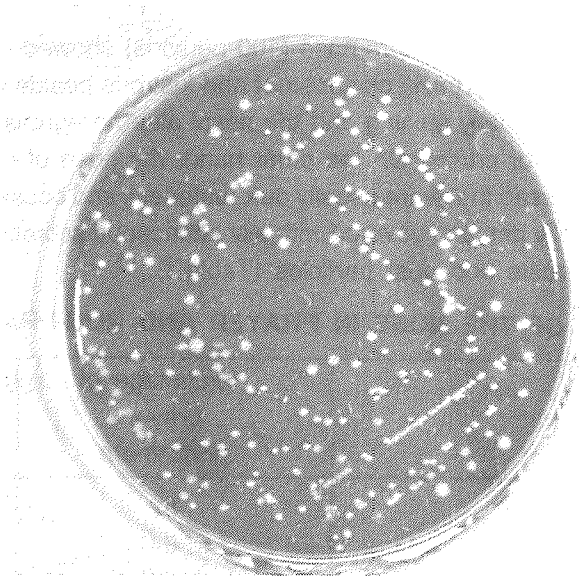

Fig. 7: Blood agar plate, cultured from non-prayer performers swabs, showing diffuse growth of bacterial colonies.

The prayer performers group, whose first swabs were taken at mid-day just before ablution, where the nose was not yet washed, showed also variety of organisms, but less in incidence, amounts and types than the non-prayer performers swabs. We got the following picture arranged according to the frequency of incidence. Staphylococci in 68% (*Staph. aureus* 42% and *Staph. albus* 26%), *Streptococci* in 14% (*Strept. viridans* 12%, *Strept. pneumonia* 2% and *Strept. pyogenes* 0%), *Diphtheroid bacilli* in 12%, *Klebsiellla pneumonia in* 4%, *Neisseria saprophytic* in 2%, and no cultures of *Escherichia coli* or other rare types. The sterile cases in this group were 20% (Fig. 8, 9, 10, 11 and 12).

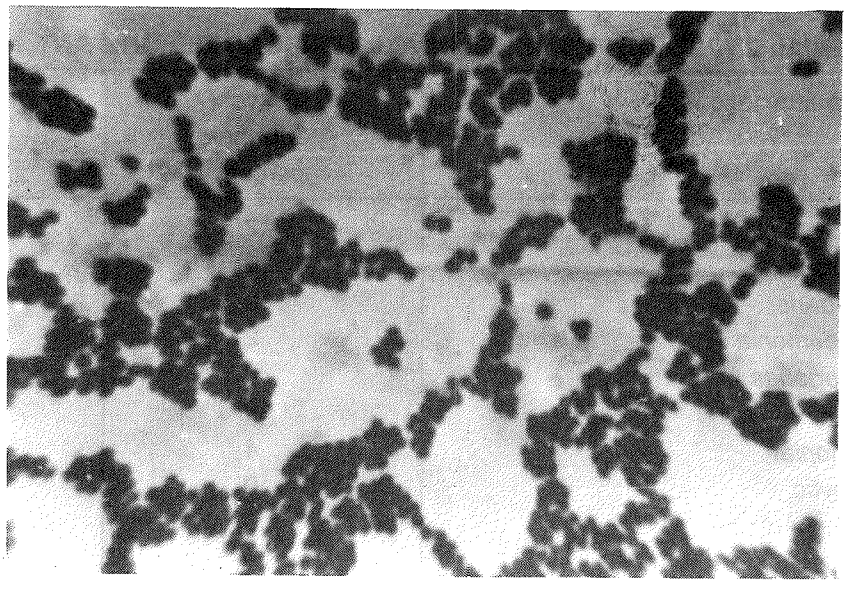

Fig. 8: Microscopic picture of Staphylococci organisms as seen in nasal swabs.

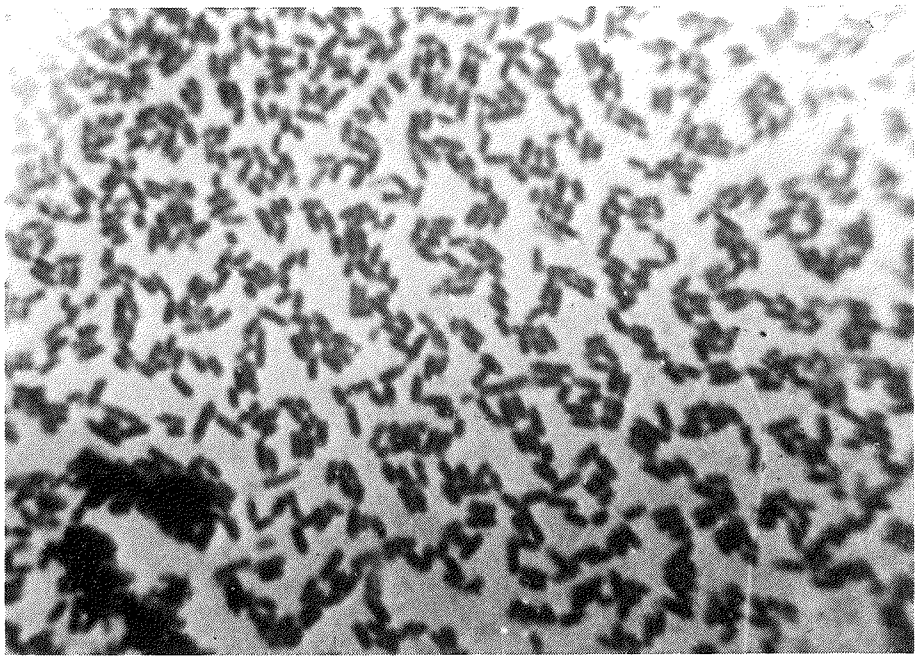

Fig. 9: Microscopic picture of Diphtheroid bacilli as seen in nasal swabs.

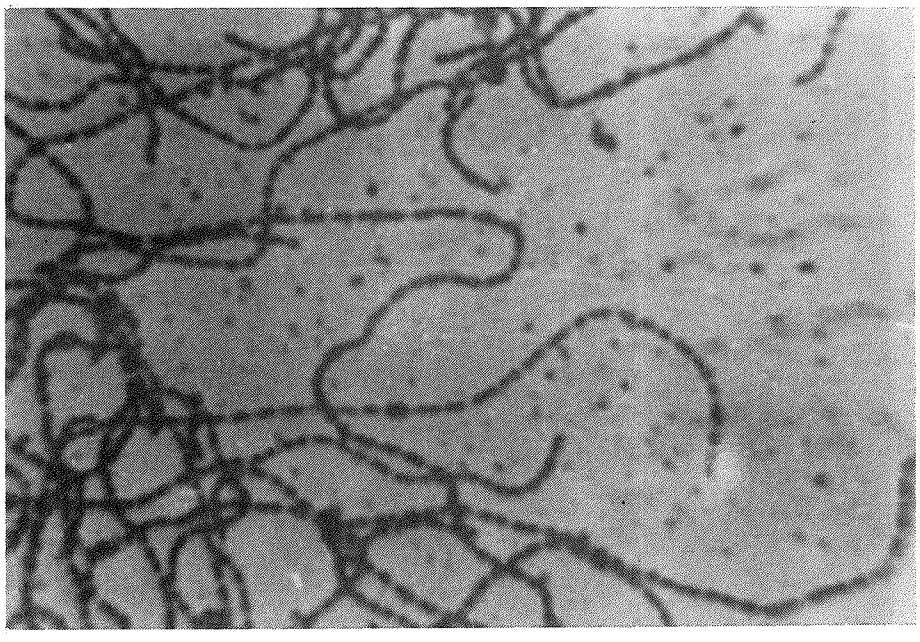

Fig. 10: Microscopic picture of Streptococci as seen in nasal swabs.

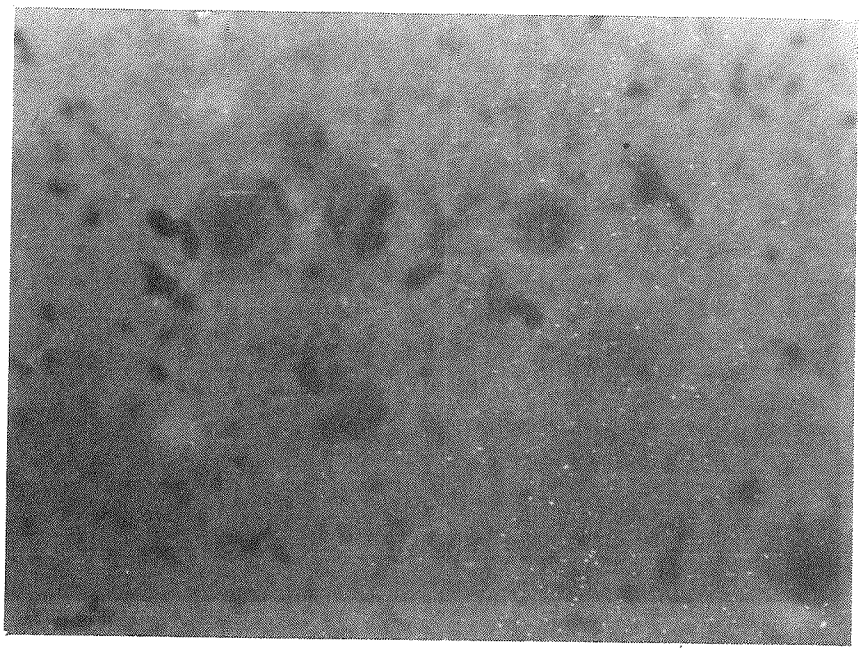

Fig. 11: Microscopic picture of Pneumococi as seen in nasal swabs.

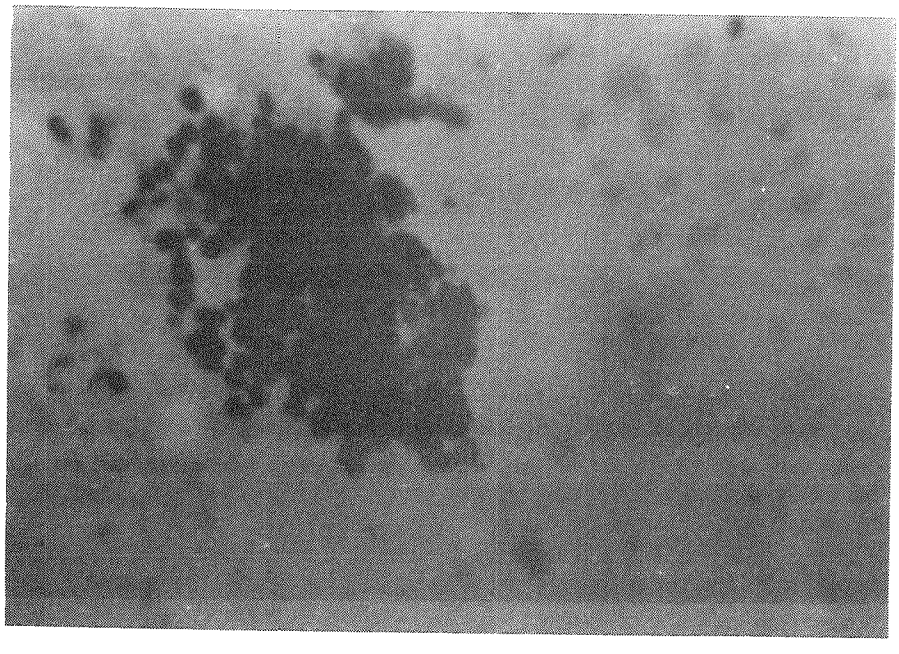

Fig. 12: Microscopc picture of Neisseria organisms as seen in nasal swabs.

Examination of the swabs taken immediately after ablution were strikingly different and of valuable importance as they differed in all aspects from the previous results. We got the following figures of the studied cases. Staphylococci in 48% (*Staph. aureus 36%* and *Staph. albus* 12%) Streptococci in 4% (*Strepto. viridans* 4%, no *Strept. pneumonia* and no *Strepto. pygenes), Diphtheroids bacilli* in 8%, *Klebsiella pneumonia* in 2%, no *Neisseria saprophytic,* no *Escherichia coli,* and no other types of bacteria. The sterile cases jumped to a high figure reaching 42% of the studied persons (Table 3 and Fig. 13)

The density of all types of bacteria dropped markedly in all prayer performers cultures, compared to the higher densities of bacterial colonies in non-prayer performers plates. This valuable finding can be demonstrated quantitatively by adopting the Box et al method of counting the bacterial colonies in the culture plate.[24] If we take the most prevailing organism in the studied groups as an example, it will be the *Staphylococcus aureus,* which was present in 64% of non-prayer performers in a high density, mostly of the +++ and ++++ degrees, and only in 36% of the prayer performers in small amounts of the + and ++ degrees only (Table IV).

TABLE III: BACTERIAL TYPES OF NASAL ORGANISMS IN PRAYER PERFORMERS AFTER ABLUTION AND THE NON-PRAYER PERFORMERS WITHOUT NASAL WASHING.

Nasal bacterial contamination	Prayer performers percent	Non-prayer performers percent
Staphylococcus aureus	36	64
Staphylococcus albus	12	30
Streptococcus viridans	4	14
Streptococcus pneumonia	0	6
Streptococcus pyogenes	0	2
Diphtheroid bacilli	8	20
Klebsiella pneumonia	2	12
Neisseria saprophytic	0	6
Escherichia coli	0	2
Proteus vulgaris	0	2
Sterile	42	4

TABLE IV: DENSITY OF THE COMMONEST ORGANISM (*STAPH. AUREUS*) IN PRAYER AND NON-PRAYER PERFORMERS.

Density	Prayer performers	Non-prayer performers
+	23	8
++	13	16
+++	0	22
+++	0	18
Total	36%	64%

The three complementary bacteriological examinations that were done to prove the importance of ablution as suggested and described by Islam gave significant results of scientific importance. Swabs taken from the nose of some studied persons who were allowed to wash the nose without hand washing showed good deminution of all types and amounts of nasal flora, but in two cases it showed the appearance of *Escherichia coli* organisms that were not present in their nose before its wash. This denotes a new nasal contamination obtained by the use of the un-washed hands (Fig. 14).

The second complementary testing was a group of swabs taken from the nose of prayer performers after nasal washing that was done once, twice or three times at ablution. The bacteriological results revealed that the nose became less contaminated or even sterile after the third water inhalation (Fig. 15).

The third auxillary testing was the bacteriological examination of water used in ablution before and after its use. The examined specimens showed that the clean water that was nearly sterile before use became contaminated by all varieties and species of nasal flora. This reveals the importance of repeated nasal washing to get rid of the heavy nasal contamination.

The examined swabs that were taken several hours after ablution showed gradual increase in the incidence and amount of nasal flora, that returns to its original state in an average of four hours. This is usually the average time period for the next ablution.

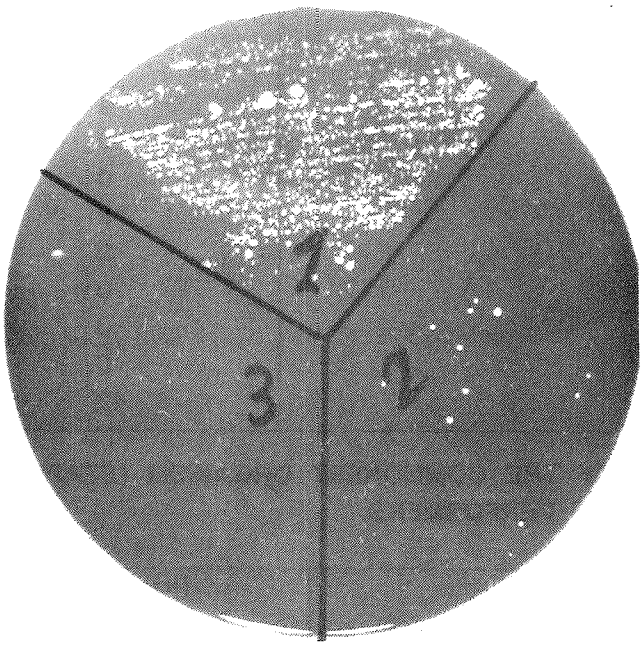

Fig. 13: Blood sugar plate with growing bacterial colonies
1. Before ablution
2. During ablution
3. After ablution

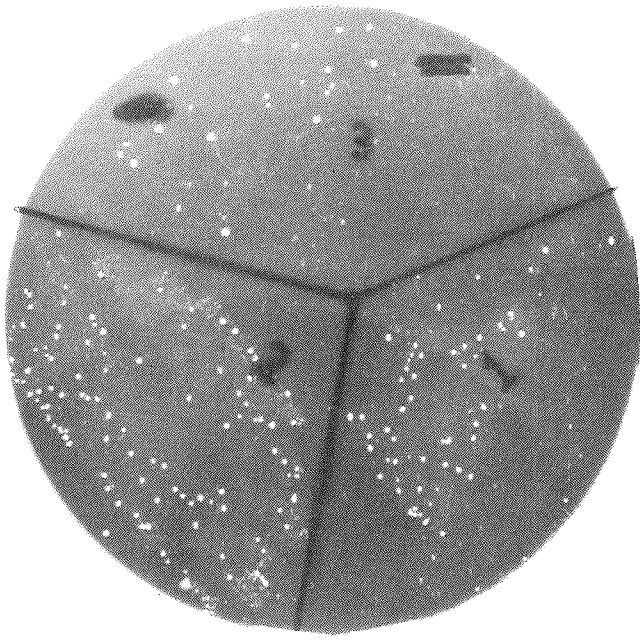

Fig. 14: Blood agar plate with growing bacterial colonies.
1. Before ablution
2. After nasal washing only
3. After hand and nasal washing as done in ablution.

DISCUSSION

Bacterial contamination of the skin and mucous membrane has received the attention of many workers in recent years[3,4,5,8]. These studies dealth with the different bacteriological aspects of the subject. Hence these works searched for the different sites of dense contamination on the skin and its orifices[5], the exact location of bacterial groups on the skin layers and mucosal surfaces[9] and the mode of transmission of these organisms from the nose and skin to other parts of the body[3,4]. The different groups and species of bacteria living on the skin and inside the nasal cavity were verified, named and classified by many workers[8,9].

The different ways of bacterial elimination were previously discussed by many authors. Skin washing as hand scrubbing, bathing and skin cleansing were the subject of some researches[10, 11, 12]. The research was so detailed as to enumerate the bacteria on selected surfaces of the skin before and after washing by water[13, 14, 15]. The effect of the different antiseptics and personal habits on the variability and density of nasal bacteria was also studied.

No previous researches concerning the effect of nasal washing by water on its bacterial contamination were carried out. Although nasal washing would be similar in effect to that of skin washing in diminishing the amounts and types of surface bacteria, no one has put that under research or experimental trials.

Islam, the last heavenly message to people, legislated the process of ablution before any prayer, where the nose is washed at each ablution by water inhalation followed by blowing the nose three successive times[6,7]

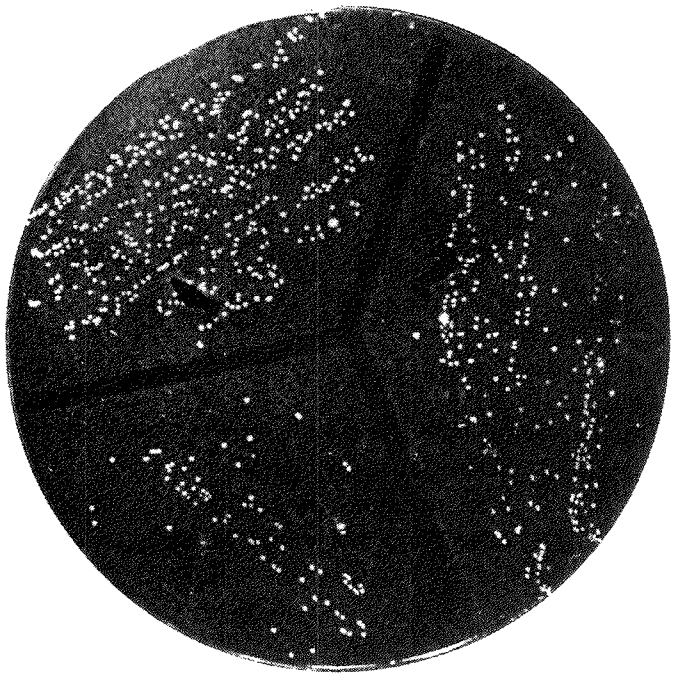

Fig. 15: Blood agar plate with growing bacterial colonies
1. After one nasal washing
2. After two nasal washings
3. After three nasal washings as done in ablution

This cleaning process was requested by Islam from all moslems 14 centuries ago, when bacteria were not yet discovered and the hygienic effects of nasal washing were not yet verified.

This present research done over two years on a considerable number of persons can be considered the first of its type, where the nose of prayer performers is exposed to such type of bacteriological investigation to study the effect of nasal washing as done in ablution on the bacteriological spectrum of the nose.

The study revealed its importance and great interest from its preliminary results when the noses of prayer performers showed marked deminution of the types and amounts of bacteria, even before ablution, than the non-prayer performers.

The decisive hygienic importance of ablution became very evident in the bacteriological cultures done after ablution, where the sterile cases became 42% (in comparison to 4% in non-prayer performers). The bacteriological types became six (instead of 10 in non-prayer performers) and the bacterial density diminished to its lowest degree.

The complementary tests confirmed the beneficial sanitary effects of ablution as they showed that hand washing is essential before nasal washing to prevent contamination of the nose from the hands, repeated nasal washing at ablution is necessary to assure more cleaning of the nose or even its sterilization in a good percentage of cases, and that ablution should be repeated every few hours, on an average of four hours, to keep the nose clean all the day long. This average time is actually the intervals between the subsequent ablutions, performed daily.

This new item of work done for the first time, to study the hygienic effects of ablution on the nose, showed clearly that ablution was essential for nasal cleaning and a subsequent control of bacterial transmission and protection against infective diseases. Undoubtedly it shares in deminution of suppuration of wounds and surgical operations and also minimises the risk of bacterial infection to the body surface and internal organs.

SUMMARY AND CONCLUSIONS

The human nose is a large reservoir of bacteria that transmits its organisms to the air, skin and the inside organs of the body. This source of infection was well studied by many workers and proved to be responsible for hospital ward infections, wound sepsis and many other diseases.

Although the nose has its own defensive mechanisms, it cannot deal with this high degree of continuous contamination and a sort of personal nasal hygiene should be adopted. For this reason the religion of Islam, advised its followers to care about their nose.

A clinical and bacteriological study was done in two years period that included two hundred persons representing two equal similar groups of regular prayer performers and non-prayer performers, which gave clinical and bacteriological data of great importance that proved the value and importance of ablution in clearing the nose from its contamination and protecting the body from many injurious micro-organisms.

The study showed the importance of hand washing at the start of ablution, the necessity of frequent nasal inhalation of water then its sniffing and the demand for frequent ablution, five times every day to keep the nose as clean as possible.

ACKNOWLEDGEMENT

The author would like to present his sincere gratitude and thanks to all volunteers, who came-willingly-and put themselves under examination and study to perform this tedious research work.

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THE EFFECT OF HONEY ON PATHOLOGIC LIVER

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INTRODUCTION

God says in the Holy Quran in Al-Nahl (Bees) paragraph 68 and 69 what means:

> *GOD HAD SENT A HOLY MESSAGE TO BEES TO MAKE USE OF THE MOUNTAINS, TREES AND SPREADING FRUITS AND GO THROUGH ALL THE ROUTES THAT GOD HAS FACILITATED. OUT OF THEIR BELLIES GETS A SYRUP (HONEY) IN DIFFERENT COLOURS; IT GIVES CURE TO PEOPLE. IN THIS, THERE IS A VIRTUAL EXAMPLE TO THINKING PEOPLE.*

Our Prophet Mohammed (ﷺ) also mentioned.

"Take these two curatives: honey and the Quran"

Honey was known to the ancient Egyptians and they called it: the holy drink. It was described in Ebers Papyrus which was written in the first dynasty 2270 years B.C. (Kamal, 1964). Ancient Egyptians recognised the medical value of honey and used it in the treatment of many diseases.

Arabs discovered the value of honey since the beginning of Islam. It was also described by Elhafez Alzahaby in his book "Al-Tibb Al-Nabavi" in the seventh Hegry century. He recommended its use for the treatment of liver, kidney and gastro-intestinal diseases. Ibn Albitar similarly described it in "Mofradat El-Adwiya" in the thirteenth century.

In the sixteenth century, Dawood Elantaky in his book advocated its use in the treatment of jaundice and hepatotoxic diseases.

Honey is used as a vehicle for medicines, such as honey cough syrups. Some physicians have recommended honey with milk for feeding infants especially those suffering from rickets, scurvy, malnutrition, anemia, inflammation of the intestine and the effects of prematurity. For athletes and others engaging in strenuous physical labours honey has been widely used: since the dextrose portion of honey is quickly absorbed into the blood stream while the levulose must be changed first to glycogen and then into dextrose, honey provides an immediate as well as an extended source of energy. This particular characteristic of honey is the basis for its recommendation by some doctors for diabetics.

Fresh honey is composed of the following constituents:

Water	17.70%
Levulose (fruit sugar)	40.50
Dextrose (grape sugar)	34.02
Invert sugars	74.98
Sucrose (cane sugar)	1.90

Dextrins	1.51
Ash (minerals)	0.18
Acid	0.08
Undetermined	4.9

This gave us impetus to investigate effect of honey on the pathologic liver in an experimental model.

MATERIAL AND METHODS

Forty male albino rats weighng 180 to 200 grams were equally divided into four groups, each group consisted of ten animals. Estimation of serum glutamic pyruvate transaminase (SGPT) and serum glutamic oxalacetate transaminase (SGOT) was carried out for all animals in the four groups at the start of the experiment.

Group 1: Induction of hepatotoxicity was carried out in each animal by oral administration of 5 ml./Kg ethyl alcohol followed 18 hours later by intraperitoneal (i.p.) administration of carbon tetrachloride in the dose of 0.5 ml/Kg body weight. Afterwards the liver function tests were estimated and the animals were observed for 15 days without receiving any treatment.

Group 2: Hepatotoxicity was induced in the animals as previously mentioned in group 1. Then liver function tests were estimated subsequently, each animal received 2 ml distilled water orally by gastric cannula for 15 days.

Group 3: Hepatotoxicity was induced in all animals as aforementioned. Then liver function tests were carried out for all the animals. Afterwards, each animal received 5 ml/Kg body weight fresh clover honey orally daily for 15 days by gastric cannula.

Group 4: Hepatotoxicity was induced in all animals as mentioned before and liver function tests were estimated. Then each animal received orally, 50 mg/Kg of thiazolidine-4-carboxylic acid (Heparegen) in distilled water for 15 days.

At the end of the experiment the survival rate in each group was counted. Estimations of SGPT and SGOT were carried out in living animals. The livers of the animals in each group were dissected out and sent to the pathology department for examination.

RESULTS

The results are shown in table 1.

TABLE 1
THE EFFECT OF HONEY ON HEPATOTOXICITY IN COMPARISON WITH HEPAREGEN

Group Parameter	Group 1 1st Control	Group 2 2nd Control	Group 3 Treatment with honey	Group 4 Treatment heparegen
Induction of hepato-toxicity	—	—	Oral 5ml /kg C_2H_5 0.5 ml/kg CCl_4	Oral 15ml/kg C_2H_5 +I.P. 0.5ml/kg CCl_4
x SGPT at Start of experim.	19	18	18	20
x SGOT at Start of experim.	50	54	52	54
x SGPT after induced hepatotoxicity	45	38	35	40
x SGOT after induced hepatotoxicity	105	104	110	115
x SGPT after treatment by honey 5ml/kg orally for 15 days	—	—	15	—
x SGOT after treatment by honey	—	—	60	—
x SGPT after treatment by Heparegen 50 mg/kg orally for 15 days	—	—	—	30
x SGOT after treatment by Heparegen	—	—	—	82
Survival Rate	0%	0%	90%	40%

DISCUSSION

A successful experimental model for hepatotoxicity was established in this study by the combined administration of ethyl alcohol and carbon tetrachloride. Carbon tetrachloride is one of the most important hepatotoxic agents (Recknagel 1967).

It can produce both acute hepatic necrosis and fatty liver degeneration (Klassen and Plaa, 1966; Judah, 1969; Fowler, 1970; Grice et al., 1971). Moreover, it can affect various cell organelles such as the endoplasmic reticulum, the mitochondria and the lysozomes (Bassi, 1960, Dianzani, 1963, Ashworth et al, 1963). Ethyl alcohol as well is a strong hepatotoxic agent and can induce acute hepatic necrosis (Rouiller, 1964). The basic mechanism underlying fatty liver degeneration induced by carbon tetrachloride is the blockade of the secretion of hepatic triglyceride into the plasma (Lombardi, 1966). On the other hand, the mechanism of acute hepatic necrosis is the dilatation of the endoplasmic reticulum and the inhibition of protein synthesis (Magee, 1966).

Ethyl alcohol or ethanol is also considered as a hepatotoxic agent that is able to produce fatty degeneration in the liver. Ethanol ingestion, both acute and chronic, affects lipid metabolism resulting in the accumulation of triglycerides in the liver (Lieber, 1967). There is also evidence that ethanol has a direct inhibitory effect on hepatic gluconeogenesis (Krebs et al, 1969). The net result is hypoglycemia subsequent to the depletion of glycogen stores (Vartia et al, 1960).

The available model is characterised by the following criteria:

1. The administered agents produce distinctive lesions.
2. The severity of the lesions is related to the dose.
3. Quantitative differences in potency can be found but the same type of lesions can be produced in all test animals.
4. The lesions are reproducible in various experimental animals.
5. The lesions appear after a predictable brief latent period.
6. Liver function tests are seriously influenced in this model.

After induction of hepatotoxicity, the levels of serum glutamic pyruvate transaminase (SGPT) and serum glutamic oxalacetate transaminase (SGOT) markedly increased.

The significant change of these parameters is an indication of hepatic parenchymal degeneration and a sign of hepatotoxicity, (Hawk, 1965, Cornish, 1971).

The animals in the control groups began to loose weight 24 hours after the induction of hepatotoxicity and died within 15 days.

In the third group which was treated by honey for 15 days, the survival rate was 90%, and the liver function tests were restored to normal values (table 1). The curative and beneficial effect of honey can be attributed to the following.

1. Correction of hypoglycemia
2. Replenishment of glycogen stores in the liver
3. Stimulation of hepatocytes to recover from fatty degeneration

On the other hand, thiazolidin-4-carboxylic acid (Heparegen) is a new synthetic compound for the treatment of hepatotoxic conditions. It supplies the liver with exogenous sulph-hydryl group which is required for normal liver function.

This compound produced a beneficial effect on the hepatotoxic model established in this study but the liver function tests were not restored to the normal values, and only 40% of the animals survived after treatment with Heparegen. The pathological picture of the liver in groups 1 and 2 proved the hepatotoxic effect of both ethyl alcohol and carbon tetrachloride.

In the third group which was treated by honey, the pathological picture markedly improved and the hepatic cells became normal. The fourth group which was treated by heparegen showed moderate improvement in the pathological picture.

Comparison between natural honey and synthetic heparegen indicates that the first is far more superior in combating hepatotoxicity than the second, as regards the available model.

CONCLUSION

The model of hepatotoxicity applied in this study is a successful model for testing drugs and material that are devoted for treating pathological liver conditions. Fresh honey proved to have a significant curative effect against severe hepatoxicity.

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EFFECTS OF PURE HONEY FROM *APIS FLOREA* (SMALL BEE), *APIS DORSATA* (LARGE BEE) AND AN AULTERATED HONEY ON BLOOD GLUCOSE LEVELS OF NORMAL AND ALLOXAN-DIABETIC RABBITS

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INTRODUCTION

To lessen the risk of cardiovascular disease, American, Canadian and British diabetes associations have recently recommended increasing the carbohydrate intake by the diabetic patients. They have agreed on the point that foods which raise the blood glucose level least for a given carbohydrate content are most suitable (Jenkins *et al.*, 1983). These considerations have raised the question as to what particular carbohydrate rich foods should be recommended to the patients suffering from diabetes.

Honey, the largest portion of which consists of sugars has been considered not only to be non-injurious but also a cure for diabetic patients (Grout, 1954). It is frequently used as a sweatening agent in place of sucrose in eastern folk antidiabetic preparations. Moreover, it has been regarded empirically even as a hypoglycaemic agent in the indigenous medicine (Nadkarni, 1954; Said, 1969). The present investigations were, therefore, carried out to determine the chemical analysis of three different honeys and to study their effects on the blood glucose levels in normal and diabetic albino rabbits.

MATERIALAS AND METHODS

Chemicals Used

Alloxan-monohydrate, alpha-D-glucose (anhydrous), methanol and potassium sodium tartrate were obtained from B.D.H. Laboratories (Chemical Division), Poole, England. Glacial acetic acid, benzoic acid, O-toluidine, thiourea, DNS (3, 5 dinitro salicylic acid) and trichloracetic acid were obtained from E. Merck Darmstadt, West Germany. All other chemicals and reagents used were of analytical grade prepared by E. Merck or B.D.H. Laboratories. Tolbutamide was obtained from Hoechst (Pakistan) Ltd., Karachi.

Animals Used

Adult, healthy rabbits of a local strain weighing between 1000-1500 g were used in these experiments. The animals were kept in an air-conditioned animal room of the Physiology and Pharmacology department of the University. The animals were offered a balanced rabbit feed prepared by the Nutrition department of the University and allowed tap water *ad libitum.* The effects of honeys were studied on blood glucose levels on the normally fed (non-fasted) rabbits. In addition, separate experiments were performed to study the effects on blood glucose levels of the non-fasted alloxan-treated diabetic rabbits.

Preparation of Diabetic Rabbits

A group of rabbits, weighing 1000-1500 g were made diabetic by injecting them intravenously with 150 mg/kg body weight of alloxan monohydrate (Akhtar *et al.,* 1981). Eight days after injection of the alloxan monohydrate, blood glucose levels of all the surviving rabbits were determind by the O-toluidine method as described by Fings *et al.,* 1970. Rabbits with blood glucose levels of 350-550 mg/100 ml were considered as diabetic and were employed for further study as already reported by Sharma *et al.* (1978).

Honeys Used and Determination of their Chemical Composition

Honeys from small bee *(Apis florea)* and large bee *(Apis dorsata)* were obtained from a village of Punjab. The samples were collected in pure form directly from the honey-combs and were preserved in glass jars after proper processing. Similarly, a low priced honey sample was purchased from the market of Faisalabad. All the samples were analysed chemically for their mineral contents (ash), moisture, total reducing sugars and non-reducing sugar contents. The said contents of all the three honey samples were determined by the procedures described in AOAC (1980).

Grouping of Rabbits

The rabbits were randomly divided into different groups or sub-groups of 6 animals each. Animals of group I to IV were normal and healthy (non-diabetic), while the animals of the group V to VIII were made diabetic by administering alloxan-monohydrate as described earlier in a sub-heading. Group I served as a untreated control as they received orally 20 ml of water (Marquis *et al.,* 1977). The animals of groups II to IV were treated orally with 5 ml, 10 ml and 15 ml/kg body weight of honey diluted upto 20 ml/kg with the distilled water. The animals of group V and VI were treated with tolbutamide (250 mg and 500 mg), a standard hypoglycaemic agent. Similar grouping was followed for testing all the 3 types of honeys.

To test the effect of honeys on hyperglycaemic animals the alloxan-diabetic rabbits were made similar grouping. Animals of group V were kept as diabetic control and were administered 20 ml of water only. The group VI to VIII were treated orally with 5 ml, 10 ml, and 15 ml/kg body weight of honey diluted upto 20 ml with the distilled water. Similar grouping was followed for testing all the 3 types of honey in diabetic animals.

Preparation and Administration of Honeys and Tolbutamide

The amount of honey required for each animal was calculated on body weight basis and the required amount of honey was weighted by using an electronic balance. This was well mixed with water and the final volume was always made upto 20 ml. The honey solution obtained was then administered orally to each animal by using stainless steel feeding needle connected with 30 ml (B.D.) record syringe. Similarly the amount of tolbutamide required by each rabbit was calculated and the amount was drawn from the tolbutamide injection (Rastinon) and diluted to 20 ml. This solution was then administered orally by the method described above.

Collection of Blood

Just after drug administration, the animal was held in a wooden rabbit holder and immediately 0.1 ml of blood was collected from the saphenous vein. Smilarly, samples for blood glucose were collected at 4, 10 and 24 h after drug administration. After pricking the vein with a needle, the blood was collected with a 0.1 ml blood sugar pipette. After collection of blood, the pricked site of the vein was pressed with a cotton swab soaked with 70% ethyl alcohol to protect the rabbit against infection.

Determination of Blood Glucose Levels

Blood glucose was determined by the method of Fings *et al.* (1970) using the O-toluidine reagent. This method gives results very close to the glucose oxidase method and is one of the most widely used manual methods.

Statistical Analysis

Mean blood glucose levels were expressed as mg/100 ml ± SEM in all the experiments and Students' "t" test was used to check their significance.

RESULTS

Chemical Analysis of Honeys

Table 1 shows the composition of all the three types of honey used. It shows that their ash contents were 0.611 g%, 0.505 g% 0.303 g% for *Apis florea, Apis dorsata* and low-priced commercial honey, respectively. Since the proposed Codex (1969) standard's requirement of ash contents is 0.6 - 1.0%, the commercial honey tested has been found to possess lower ash contents as compared to the natural honey. The reason for the sub-normal ash contents of the low-priced commercial honey might be the mixing of some artificial honey to some natural one. By doing this though the volume of honey might have increased but the total content of a naturally occurring substance such as ash must have decreased. Moisture contents of the honeys used did not exceed the limits and were not liable to fermentation. The principal constituent of honeys was found to be the reducing sugars which were within the recommended limits. By the addition of super saturated sucrose solution to a natural honey would increase its volume but will not significantly affect its contents of reducing sugars. The non-reducing sugars contents were 5.16 g%, 5.50 g% and 9.60 g% for *Apis florea, Apis dorsata* and low-priced commercial honey, respectively. It is well established that the non-reducing sugar in the honey is maximally sucrose. Its value in low-priced commercial honey was found to be quite high which clearly indicated that sucrose was added to some natural honey. Nevertheless the non-reducing sugars of natural honey from *Apis florea* and *Apis dorsata* used in this study were approximately according to the standard.

TABLE 1: CHEMICAL COMPOSITIONS OF HONEYS OF *APIS FLOREA, APIS DORSATA* AND A LOW-PRICED COMMERCIAL HONEY

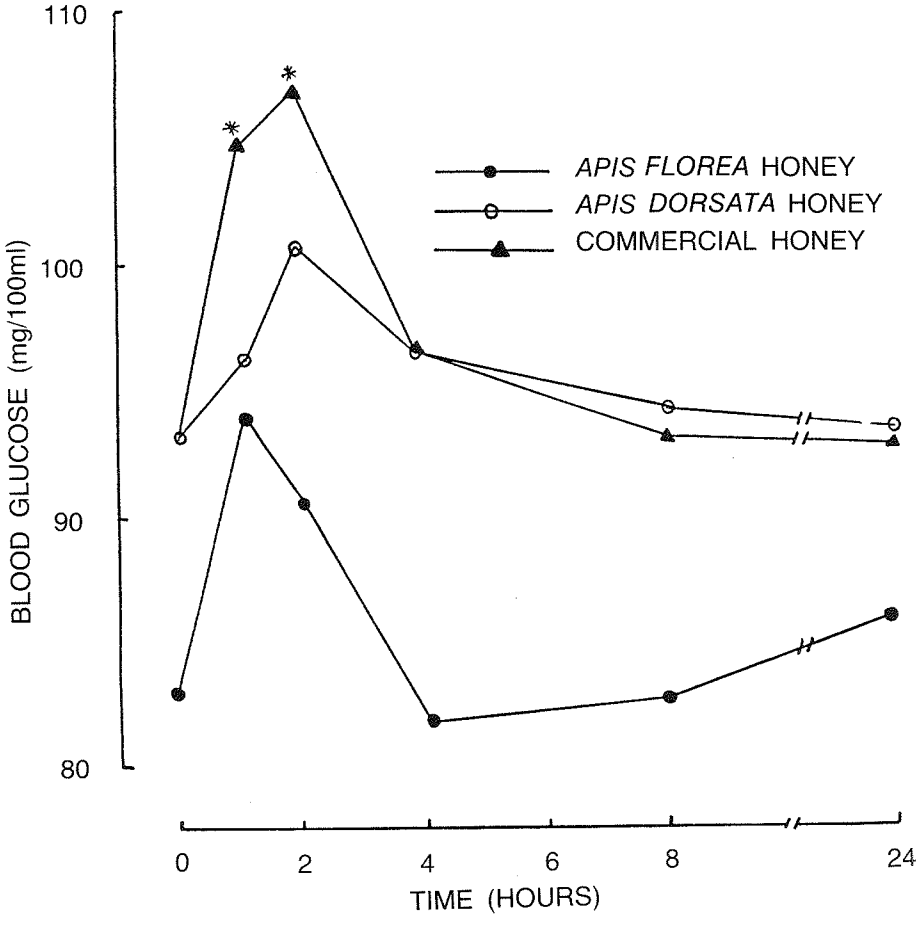
Contents	Types of Honey		
	Honey of *Apis florea* (Small-Bee Honey)	Honey of *Apis dorsata* (Large-Bee Honey)	Low-Priced Commercial Honey
	(g%)	(g%)	(g%)
Ash	0.611	0.505	0.303
Moisture	20.16	19.05	19.10
Total Sugars	70.05	70.30	76.72
Reducing Sugars	64.89	64.80	67.12
Non-Reducing Sugars	5.16	5.50	9.60

Each value is the mean of at least 3 estimations.

Effect of Graded Doses of Honeys on Blood Glucose Levels in Normal Rabbits

The mean blood glucose concentrations ±SEM of honey-treated rabbits after oral administration of different doses of all the three honeys at various time intervals are shown in Figure 1 - 3. Blood glucose levels of rabbits treated with 20 ml water at zero hour after administration was found to be statistically the same ($P > 0.05$) at all intervals. The blood glucose level of animals treated with 5 ml/kg of small bee honey at zero hour interval after drug administration was 83 ± 3.9 mg/100 ml. The honey slightly increased blood glucose levels at 1 and 2 hours. This increase was, however, found to be statistically non-significant ($P > 0.05$) from the zero hour level as well as from their preceding value. Glucose level at 1, 4, 8 and 24 hour intervals did not differ statistically from the zero hour level. Similarly, administration of 5 ml/kg of large-bee honey did not significantly affect the blood glucose levels at all intervals checked. However, the commercial honey at this dosage raised ($P < 0.05$) the blood glucose at 1 and 2 hours when the post-treatment values were 105 ± 4.03 and 107 ± 3.6 mg/100 ml of blood (Figure 1.)

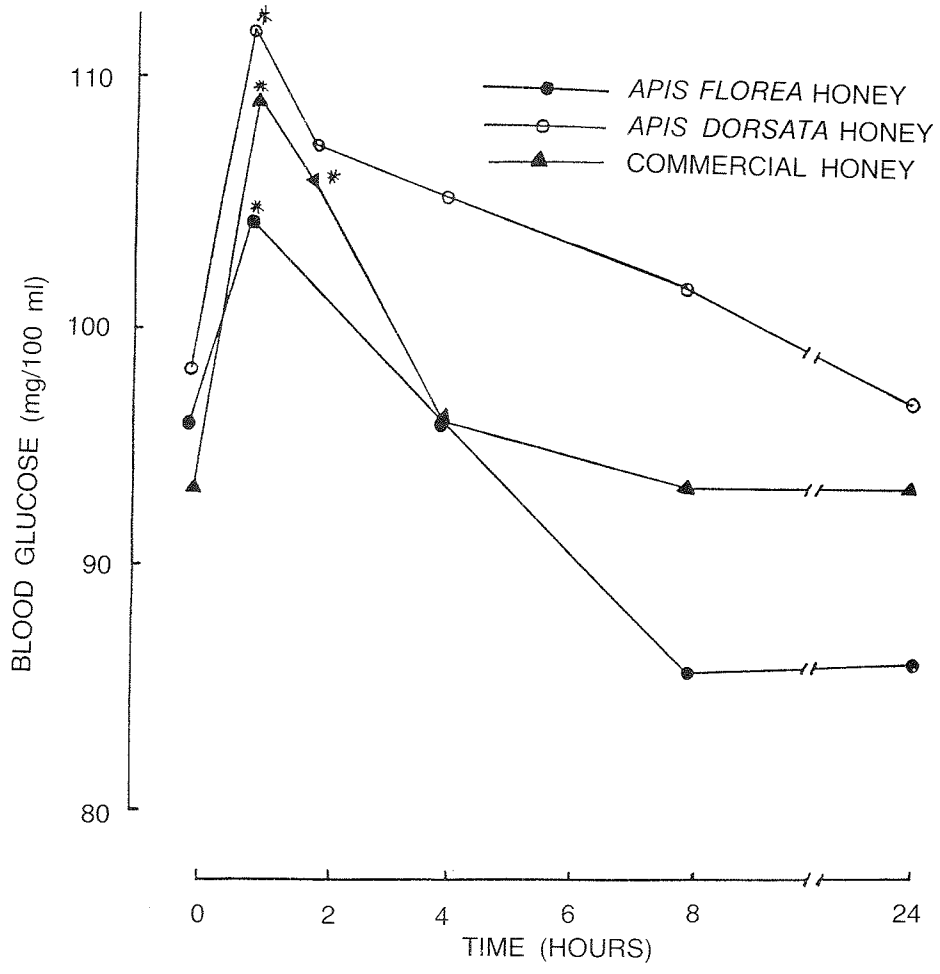
FIG. 1: BLOOD GLUCOSE LEVELS (mg/100 ml) OF NORMAL RABBITS AFTER ORAL ADMINISTRATION OF 5ml/kg OF NATURAL HONEY OF *APIS FLOREA, APIS dORSATA* AND LOW-PRICED COMMERCIAL HONEY.



⋆ — Significant difference from zero level ($p<0.05$)
All the other values are non-significantly different at ($p>0.5$) from the zero hour.
Number of animals in each group = 6.

Figure 2 shows that the mean blood glucose level of rabbits treated with 10 ml/kg of small-bee honey was found to be 96 ± 1.8 mg/100 ml just after its administration. There was increase in blood glucose level at 1 hour when the glucose level was 104 ± 2.7 mg/100 ml. It was found to be significantly higher ($P < 0.05$) than at zero hour level. However, increase at 2, 4, 8, and 24 hours was found to be non-significantly higher than the level at zero hour interval. Similarly, Figure 2 shows that the mean blood glucose level of rabbits treated with 10 ml/kg of large-bee honey was found to be 98 ± 3.1 mg/100 ml just after its administration. There was increase in blood glucose level at 1 hour interval when the glucose level was 112 ± 5.1 mg/ml. It was found significantly higher ($P< 0.05$) than at zero hour level. However, increase at 2,4, 8 and 24 hours was found to be non-significantly higher than the level at zero hour interval. The mean blood glucose level of rabbits treated with 10 ml/kg body weight of commercial honey was found to be 93 ± 4.6 mg/100 ml just after its administration. There was increase in blood glucose level at 1 and 2 hour when the glucose levels were 109 ± 3.1 and 106 ± 2.5 mg/100 ml. It was found to be significantly higher ($P < 0.05$) than at zero hour level. However, increase at 4, 8, and 24 hours was found to be non-significantly higher than the level at zero hour interval (Figure 2).

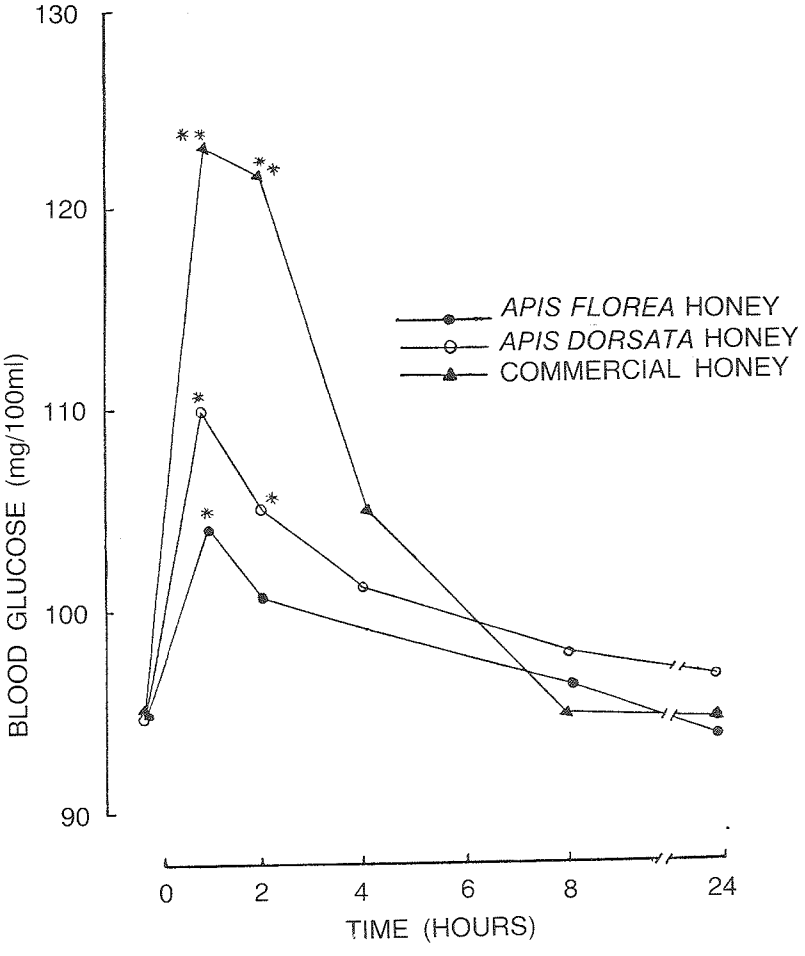
FIG. 2: BLOOD GLUCOSE LEVELS OF (mg/100ml) NORMAL RABBITS AFTER ORAL ADMINISTRATION OF 10ml/kg OF NATURAL HONEYS OF *APIS FLOREA, APIS DORSATA* AND LOW-PRICED COMMERCIAL HONEY.



⋆ — Significant difference from zero level ($P<0.05$).
All other values are non-significantly different at $P>0.05$ from the zero hour value.
Number of animals in each group = 6.

As Shown in Figure 3, the blood glucose levels of animals treated with 15 ml/kg of small-bee honey at 1 hour intervals were found to be 104 ± 2.56 which was significantly higher than at zero hour level where the level was 95 ± 2.5 mg/100 ml. The values at 2, 4, 8 and 24 hour intervals were found to be non-significantly higher than at zero hour. The blood glucose level of animals treated with 15 ml/kg of large-bee honey at 1 and 2 hour intervals were found to be 100 ± 2.9 and 105 ± 4.03 mg/100 ml which were significally ($P < 0.05$) higher than at zero hour when the level was 95 ± 3.9 mg/199 ml. The values at 4, 8 and 24 hour intervals were found to be non-significantly higher than at zero hour. The blood glucose levels of animals treated with 15 ml/kg body weight of commercial honey at 1 and 2 hour intervals were found to be 123 ± 6.8 and 122 ± 4.3 mg/100 ml which were significantly higher than at zero level where the level was 95 ± 3.9 mg/100 ml. The values at 4, 8 and 24 hour intervals were found to be non-signifcantly higher than at zero hour (Figure 3).

FIG. 3: BLOOD GLUCOSE LEVELS (mg/100 ml) OF NORMAL RABBITS AFTER ORAL ADMINISTRATION OF 15ml/kg OF NATURAL HONEYS OF *APIS FLOREA, APIS DORSATA* AND LOW-PRICED COMMERCIAL HONEY



⋆ — Significant difference from zero level ($P<0.05$).

⋆⋆ Highly significant difference from zero level ($P<0.001$).

All other values are non-significantly different ($P>0.05$) from zero hour level.

Number of animals in each group = 6.

Effect of Alloxan Administration to Rabbits

The administration of alloxan to the experimental rabbits was carried out very slowly and proper care was taken to avoid sudden death. In spite of these a few animals receiving alloxan injection suddenly died. The blood glucose concentrations of surviving rabbits were determined after eight days of injection. The rabbits with blood glucose levels above 200 mg percent were selected and divided into 12 groups of six animals each. The results of these experiments are in agreement with others who have also reported that alloxan treatment produced a severe persistent hyperglycaemia in the rabbits and rats (Marquis, *et al.*, 1977 Akhtar *et al.*, 1981; 1985).

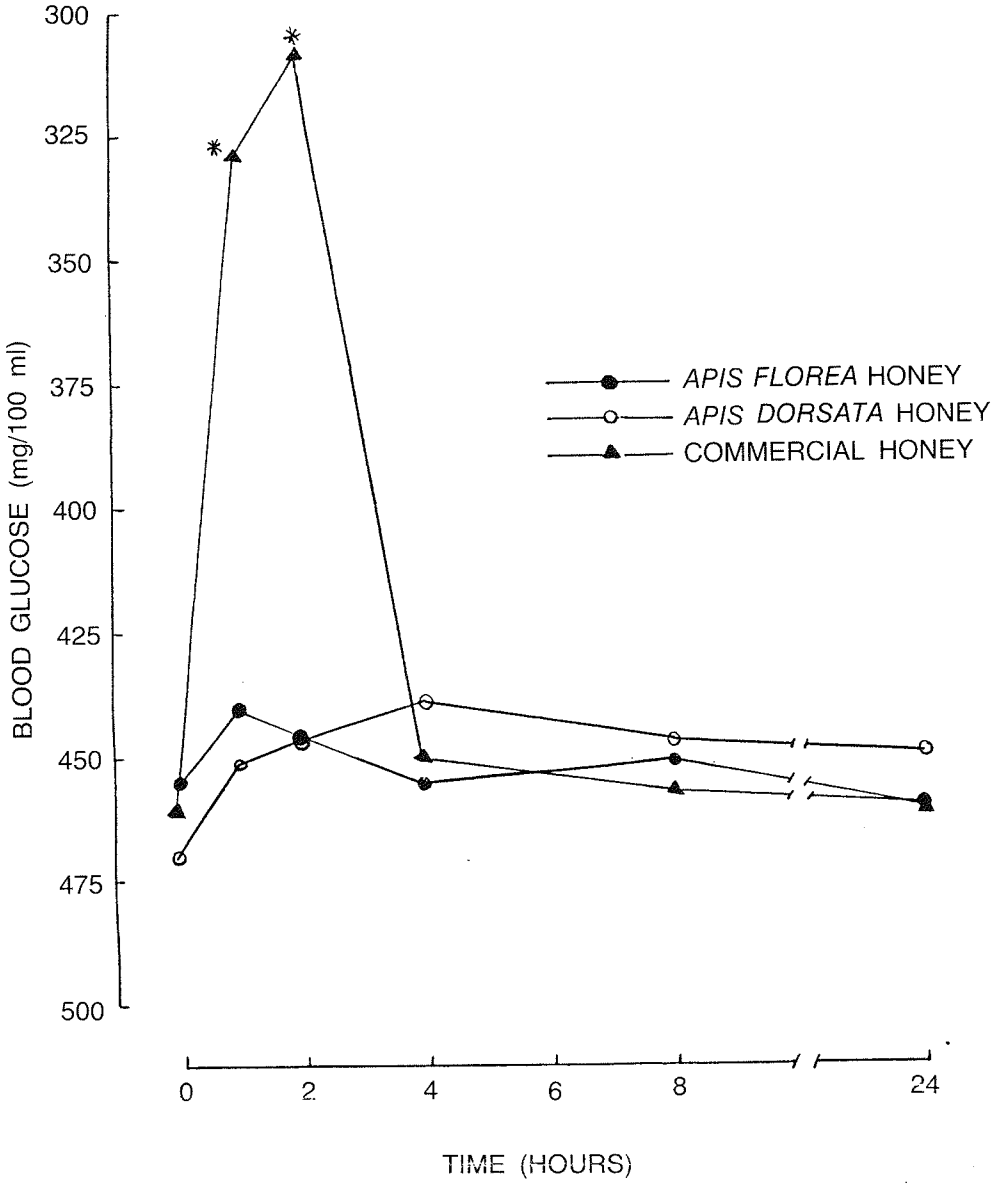
Effect of Honeys on Blood Glucose in Diabetic Rabbits

Mean blood glucose concentrations ± SEM of honeys treated alloxan-diabetic rabbits after oral administration of its different doses at various time intervals are shown in Figures 4-6. Mean blood glucose concentration of rabbits treated with 20 ml of water at zero hour intervals was found to be 342 ± 29 mg/100ml. The administration of 20 ml water alone did not alter the blood glucose levels of diabetic rabbits and their blood glucose values were to be statistically ($P > 0.05$) the same at 1, 2, 4, 8 and 24 hours intervals. Blood glucose levels of animals treated with 5 ml of small-bee honey at zero hour interval after administration were found to be 343 ± 28.3 mg/100 ml. The honey produced a slight increase in blood glucose at 1, 2, 4, 8 and 24 hours intervals, this increase was, however, statistically non-significant ($p > 0.05$). The blood glucose level of animals treated with large-bee honey at zero hour interval after administration was found to be 329 ± 29 mg/100 ml. The drug produced a slight increase in blood glucose 1, 2, 4, 8 and 24 hours intervals, this increase was however, statistically non-significant ($P > 0.05$). The level at 24 hour was 350 ± 27 mg/100 ml found to be statstically non-significant from the zero hour level as well as from the preceding values. The blood glucose levels of animals treated with low-priced commercial honey at zero hour interval after administration was found to be 339 ± 27 mg/100 ml. The honey produced a significant ($P > 0.05$) increase in blood glucose at 1 hour when the blood glucose level was 472 ± 47 mg/100 ml. The increase was, however, highly significant ($P < 0.01$) at 2 hours when the level 493 ± 35.8 mg/100 ml. The blood glucose level at 24 hour was 245 ± 28.1 mg/100 ml which was statistically non-significant ($P > 0.05$) from the zero hour level as well as from the preceding values (Figure 4).

The blood glucose levels of rabbits treated with 10 ml of small-bee honey was found to be 337 ± 27.5 mg/100 ml at zero hour. The glucose levels after 1 hour was 472 ± 47.0 mg/100 ml and that was significantly higher ($P < 0.05$) from the blood glucose level at zero hour. At 2, 4, 8 and 24 hours the levels were found to be statistically non-significant ($P > 0.05$) from zero hour level. The blood glucose levels of animals treated with 10 ml/kg of large-bee honey was found to be 329 ± 25.3 mg/100 ml. The glucose levels after 1 hour was 488 ± 44 that was significantly higher from the blood glucose level at zero hour. At 2, 4, 8 and 24 hours the level was found to be statistically non-significant from zero hour level. The blood glucose levels of animals treated with 10 ml of low-priced honey was found to be 342 ± 27.5 mg/100 ml. The glucose levels after 1 hour was 465 ± 43 and that was significantly higher from the blood glucose level at zero hour while at 2 hour interval there is highly significant increase occurring while the level was 488 ± 35.8 mg/100 ml. At 4, 8 and 24 hour levels were found to be statistically non-significant from zero hour level (Figure 5).

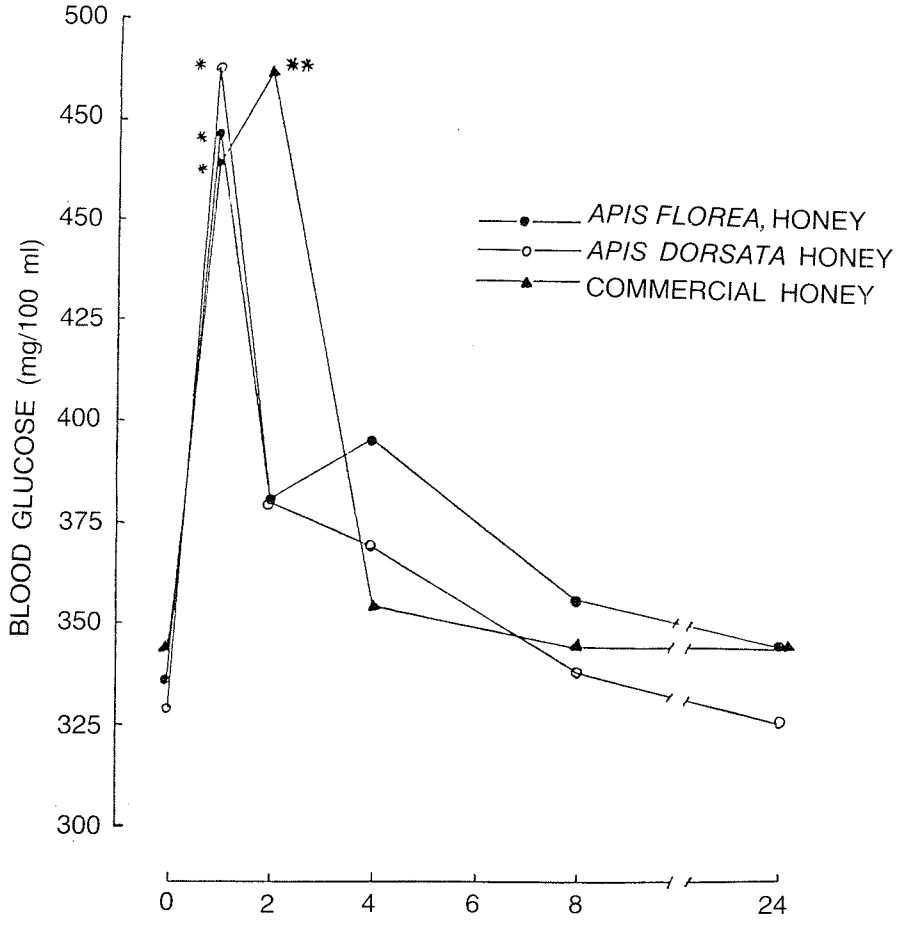
The blood glucose levels of animals treated with 15 ml/kg of small-bee honey was found to be 342 ± 29.0 mg/100 ml at zero level. The glucose levels after 1 hour was found to be 469 ± 35.0 mg/100 ml which was significantly higher ($P < 0.05$) than the blood glucose level at zero hour. At 2, 4, 8 and 24 hour levels were, however, found to be statistically non-significant ($P > 0.05$) from zero hour level. Similarly, the blood glucose level of animals treated with 15 ml/kg of large-bee honey was found to be 333 ± 26 mg/100 ml at zero hour. A

FIG. 4: BLOOD GLUCOSE LEVELS (mg/100 ml) OF ALLOXAN DIABETIC RABBITS AFTER ORAL ADMINISTRATION OF 5 ml/kg OF NATURAL HONEYS OF *APIS FLOREA*, *APIS DORSATA* AND LOW-PRICED COMMERCIAL HONEY



⋆ — Significant difference from zero level ($P<0.05$)
All the other values are non-significantly different at $P>0.05$ from the zero hour.
Number of animals in each group = 6.

FIG. 5: BLOOD GLUCOSE LEVELS (mg/100ml) OF ALLOXAN DIABETIC RABBITS AFTER ORAL ADMINISTRATION OF 10 ml/kg OF NATURAL HONEYS OF *APIS FLOREA*, *APIS DORSATA* AND LOW-PRICED COMMERCIAL HONEY.



⋆ = Significant difference from zero level ($P<0.05$)

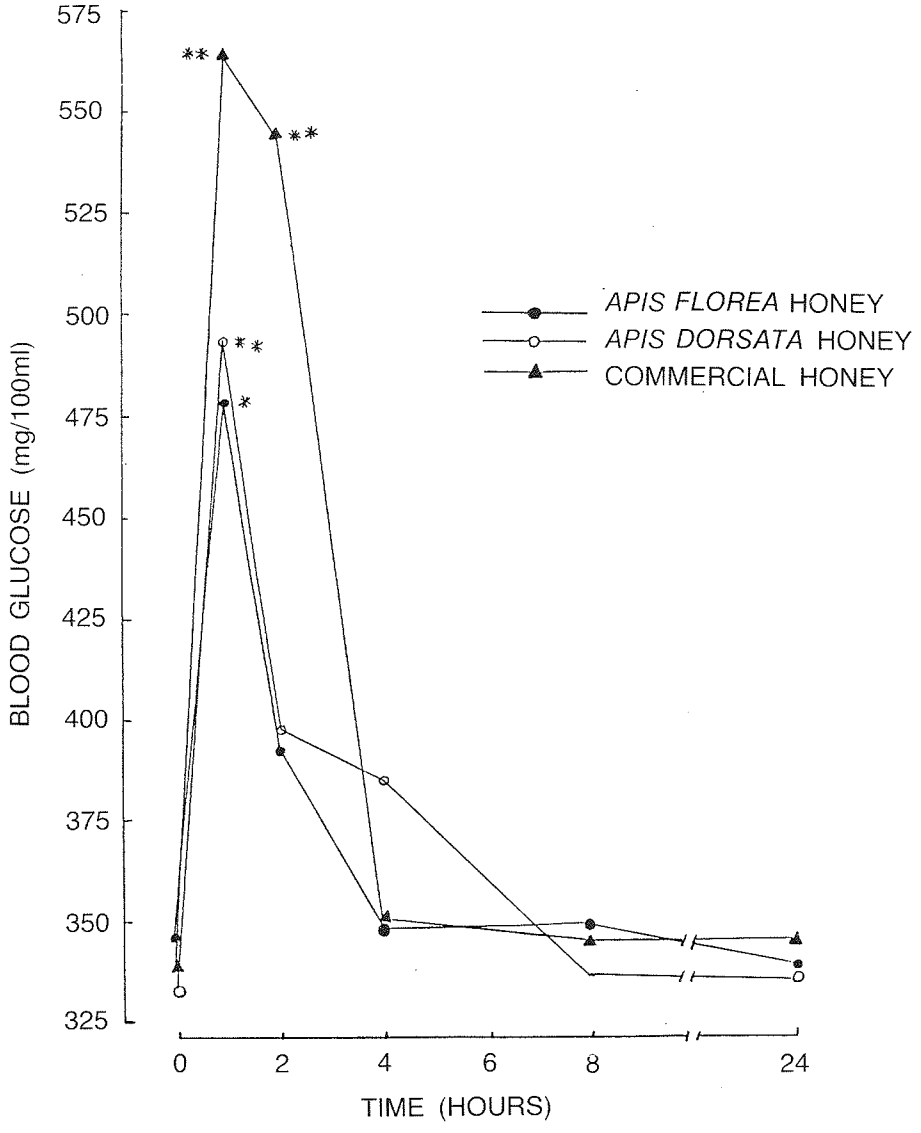
⋆⋆ = Highly significant difference from zero level ($P<0.001$)

All the other values are non-significantly different at $P>0.05$ from the zero hour.

Number of animals in each group = 6

highly significant increase in glucose level was recorded at 1 hour intervals when the glucose level was 492 ± 44 mg/100 ml. At 24 hour interval glucose level was found to 335 ± 25.5 mg/100 ml which was statistically similar to the zero hour level. The blood glucose level of animals treated with 15 ml/kg of commercial honey was found to be 339 ± 27.8 mg/100 ml at zero hour. A highly significant increase in glucose values were 569 ± 51.6 and 544 ± 43 mg/100 ml respectively. At 24 hour interval glucose level was found to be 344 ± 28.1 mg/100 ml which was statistically similar to the zero hour level (Figure 6).

FIG. 6: BLOOD GLUCOSE LEVELS (mg/100 ml) OF ALLOXAN DIABETIC RABBITS AFTER ORAL ADMINISTRATION OF 15 ml/kg OF NATURAL HONEYS OF *APIS FLOREA, APIS DORSATA* AND LOW-PRICED COMMERCIAL HONEY



⋆ = Significant difference from zero level ($P<0.05$)

⋆⋆ = Highly significant difference from zero level ($P<0.01$). All the other values are non-significantly different at ($P>0.05$) from the zero hour.

Number of animals in each group = 6.

DISCUSSION

Honey is a substance which is produced naturally by several types of bees from the nectar of various plants. Although it is sweet in taste and is known to contain certain sugars but has been claimed in the eastern medicine to exert antidiabetic properties (Said, 1969). Many practitioners of indigenous medicine (Hakims) are still using it in various formulations to treat human diabetic patients and also commonly used to sweeten the

diabetic foods and drinks. Bee keepers also claim that numerous diabetic patients have recovered from diabetes by using honey as their source of carbohydrates (Grout, 1954). It is also reported that there is indication that honey from special plant sources are more desirable for this purpose. Several international diabetes associations have agreed on the point hat foods which raise blood glucose level least for a given carbohydrate content are most suitable (Jenkins, *et al.*, 1983). As already mentioned, largest portion of honey consists of sugars but has been still considered to be non-injurious to the diabetic patients. As far as ascertained, no systemic study on the scientific grounds has been carried out to study the antidiabetic/ hypoglycaemic activity of this natural substance of high energy value derived from the plants by the bees. Therefore in the present study chemical analysis of three of honeys was carried out at first and then studied their effects on blood glucose levels after oral administration to normal (non-diabetic) and alloxan-diabetic rabbits.

The chemical analysis clearly showed that the low-priced commercial honey had the mixing of some artificial honey to some natural one. The concentrations of non-reducing sugars observed in the present studies were 5.16 g%, 5.50 g% and 9.60 g% for *Apis florea* (small-bee honey) *Apis dorsata* (large honey) and low-priced commercial honey, respectively. It is well established that the non-reducing sugar in the honey is maximally sucrose. Siddiqi and Furgala (1968), White and Hoban (1959) and several other workers have suggested that the highest limit of sucrose in the honey is 5 percent. Therefore, its value in low-priced commercial honey was found to be quite higher which clearly indicated that sucrose was added to some natural honey. Nevertheless, the non-reducing sugars in natural honeys from *Apis florea* and *Apis dorsata* used in this study were approximately according to the standard.

Blood glucose level of normal rabbits treated with 5 ml/kg body weight of the small-bee honey was found to be slightly increased at 1 and 2 hour intervals after its administration but all the values were non-significant ($P > 0.05$) from zero hour level. However, the administration of 10 ml and 15 ml/kg body weight of this type of honey significantly raised the blood glucose levels of treated rabbits only at one hour interval after which there was gradual decrease but the values at 2, 4, 8 and 24 hours were all non-significantly higher than the zero hour level (Figures 1, 2 and 3). This suggested that administration of natural small-bee honey in 10 ml and 15 ml/kg doses has raised the blood glucose levels rather than decreasing them. This is in contrast to the common folkloric belief. Blood glucose level of normal rabbits treated with 5 ml, 10 ml/kg body weight of the honey from large-bee followed similar pattern as described above except that its 15 ml/kg dose caused significant rise of blood glucose levels at 2 hour interval as well (Figure 3). In case of low-priced commercial honey, the blood glucose level of rabbits treated with 5 ml, 10 ml and 15 ml/kg body weight doses were found to be significantly raised both at 1 and 2 hour intervals. The pattern of fall however, was similar to other two honeys already described. However, its 15 ml/kg doses further increased the blood glucose level at 1 and 2 hour intervals as these values were significantly ($P < 0.01$) higher than the zero hour levels.

Figures 1-3 clearly show that the low-priced commercial honey has caused more acute hyperglycaemia. However, as evident from Figures 1, 2 and 3, fall in blood glucose levels at various doses was also acute. These data also suggest that the commercial honey has been adulterated with sucrose syrup. In contrast, confirming Augusti (1976), tolbutamide (250 mg and 500 mg/kg) was observed to produce significant hypoglycaemic effect in the rabbits at 4 hours after which the blood glucose level started rising gradually and returned to normal limits at 24 hours interval (Data not shown).

The effect of all the three types of honeys was also studied in the alloxan diabetic rabbits. Alloxan exerts highly selective cytotoxic action on the beta cells of the islets of Langerhens. The alloxan treated diabetic rabbits showed the classical signs of human diabetes, i.e. hyperglycaemia, glycosuria, polydipsia and polyurea, loss in the body weight, acidosis (Rerup, 1970). It has been reported that single intravenous injection

of 150 mg/kg of alloxan in rabbits, is effective in killing the beta cells (Butt, 1962; Laurence and Bacharch, 1964). Thus this dose of alloxan was selected for these experiments. Blood glucose level of the alloxan-induced diabetic rabbits treated with 5 ml/kg body weight of the small-bee honey was found to be slightly increased at 1 and 2 hour intervals after its administration but all the values were non-significant ($P > 0.05$) from the zero hour levels. However, the administration of 10 ml/kg of this honey significantly raised the blood glucose levels of the treated rabbits. Similar results were obtained with large-bee honey. The low-priced commercial honey produced acute hyperglycaemia in diabetic rabbits too as it did in normal rabbits.

In the light of the data discussed so far it may be concluded that, in contrast to the common belief pure natural honeys have not been found to exert hypoglycaemic effect in the rabbits. This is perhaps due to its high reducing and non-reducing sugar contents. Instead in 10 ml and 15 ml/kg doses all three honeys tested have produced a significant rise in blood glucose levels in both normal and diabetic rabbits. It has already been hypothesized that bees fed on the nectar of some specific plants produce hypoglycaemia. Therefore, it is possible that honeys used in this study were not of that nature. However, natural honeys from small and large honey-bees at low dosage of 5 ml/kg only could not produce significant hyperglycaemic effect in normal as well as diabetic rabbits. The honey adulterated with a saturated solution of sucrose produced a significant rise in blood glucose levels even at 5 ml/kg dose level in normal and diabetic rabbits. These data do suggest that pure honeys from small or large bees in low doses may be recommended as a source of carbohydrate or even employed as a sweetening agent for the diabetic patients. In large doses, however, honey in principle seems to be contraindicated as all other sugars or carbohydrate rich drinks or foods.

Finally, it must be clarified that these findings are in now way contradiction to what Allah Taala has said in the Holy Quran Sharif which means:

IN IT (HONEY) THERE IS CURE TO PEOPLES,

These words of Allah do not specify the disease or diseases but lay freedom to human thinking and experimentation in this respect. We are ourself to find out for which disease and under what circumstances it carries a cure to the people.

ACKNOWLEDGEMENT

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SUMMARY OF DISCUSSION

Prof. Abdul Hafiz Helmy enquired from Dr. Amer as to how many times the ocular pressure was measured?

Dr. Amer mentioned that it was measured twice at 10.00 A.M. and 10.00 P.M.

Dr. Abdullah Basalama enquired whether fasting has beneficial effect only on the health of the eye or the whole body and further commented that he had measured the effect of fasting on the sperms before, after and during fasting and mentioned his observations on the number and movement of the sperms.

Dr. Sleim Ammar enquired from Dr. Adil Kandil whether honey can mobilize glycogen? He further mentioned that they have done some studies on preclampsia and monitored their CFT and found that pure honey (very fresh) was good. He further asked that heavy dose of honey i.e. 5 ml/kg. was given . Was it related to human dose?

Dr. Adil M. Kandil replied that further studies will be conducted using floral, nonfloral honeys and sucrose. Regarding the dose, he mentioned that it is based on the laid down critaria for biological experimentations in laboratory animals.

Dr. Abdul Hafez Helmy commented that when we say we are not specific, it does not mean cure for everything. It depends on the kind of honey and the colour of the honey.

Dr. Abdul Aziz Kamil remarked: "I can't really speak about the meaning of cure. There are scholars who understand more than me about the term "Shifa". It is general term within the language and within the context.

Dr. Shehata suggested that Prof. Bumby should be consulted regarding the quality and colour of honeys.

Part Three: *Applied Research:*
B-Aims and Objectives of Al-Shari'ah as mentioned in Quran and Sunnah.

CHAPTER II

SOME SELECTED PAPERS - NOT PRESENTED

1. EFFECT OF RAMADAN FASTING ON BLOOD LIPIDS AND PROTEINS
   Prof. Mahmoud Abou El-Makarem, *et al*
2. HYPERPROLACTINEMIA AND POSTPARTUM ANOVULATION
   Dr. Mohd. Mostafa Badawi
3. EFFECT OF ISLAMIC FASTING ON UROLOGICAL PATIENTS
   Dr. Fahim Abdelrahim, *et al*
4. SCIENTIFIC EVALUATION OF SLAUGHTER AND STUNNING METHODS
   Prof. Farouk M. Ali, *et al*

EFFECT OF RAMADAN FASTING ON BLOOD LIPIDS AND PROTEINS

Prof. Mahmoud Abou El-Makarem, Drs. Sami Abdel Aziz, Hosni Hanafy, Farouk Saber Abdel Monem Gaballa, Ismael Hegazy and Abdel Aziz Elnokaly

EGYPT

INTRODUCTION

Fasting Ramadan is one of the pillars of Islam. During this month people do not take any food or drink during day light. Also, no smoking is allowed. This year 1985 a.c. (1405 heg.), fasting period was about 14 hours. At night, people can drink, eat and smoke.

So, Ramadan fasting is a change in habit from eating during the day to eating at night. Also, fasting for a whole lunar month may cause some changes in blood and body constituents. Yegin et al. (1983) reported no change in blood total proteins, total cholesterol, urea and uric acid during Ramadan fasting.

Total cholesterol and esterified cholesterol levels were found to vary according to the population studied. Total cholesterol level in normal control of Western population were higher (214 mg/dl) than those of Brazilians (174.4 mg/dl), (Gillet et al., 1976; Devenyi et al., 1981). Also, values for Egyptians are lower (172 mg/dl) (El Sebaei, 1985).

HDL-cholesterol is considered as a protective factor in relation to atherosclerosis (Gordon et al., 1977). Ischaemic heart diseases and atherosclerosis are more related to alterations in the percentage of HDL-cholesterol to total cholesterol (Holmes et al., 1981). Caloric depletion and undernutrition may affect HDL-cholesterol (Kanel et al., 1983). Apo-A is the major apoprotein of HDL and it lies on the surface of the particle (Mao et al., 1975). Apo-A-I and Apo-A-II constitute about 90% of total HDL protein (Levy et al., 1976). Apo-A has been found to be the specific cofactor for the lecithin — cholesterol acyl transferase (EC. 2.3.1.43) reaction in the body. Without Apo-A the cholesterol in blood stream is not esterified (Levy, 1981). Apo-B is the major protein of LDL. Apolipoproteins levels are better genetic markers than lipids for atherosclerosis (Avogaro et al., 1979).

The aim of this study is to detect whether Ramadan fasting causes any change in blood lipids especially those related to ischaemic heart diseases. Also, effects on plasma proteins and albumin will be studied as an indication of the nutritional state for the individual.

MATERIALS AND METHODS

Forty adult male Egyptian medical students (age 25.4±4.8 years) fasted 27 days of Ramadan 1405 heg. On the 28th day at 2 O'clock afternoon (this period corresponds to 12 hours fast), 10 ml venous blood was withdrawn. Blood was left at room temperature to clot. Serum was separated.

The same students were used as control. Blood samples were taken from them 4 months after Ramadan, to ensure that any change due to fasting has disappeared.

All students were chosen of the ideal weight, no history of diabetes, no smoking, no liver disease and taking no drugs. Urine samples were collected and were free of glucose and acetone.

METHODS

The following blood constituents were determined :

— Total cholesterol was determined in serum by the enzymatic method of Richmond (1973).

— HDL-cholesterol was determined according to Burstein et al. (1970). Triglycerides according to Buccolo and David (1973).

— Free cholesterol was determined as described by Leffler (1959).

— Free fatty acids (FFA) in serum were determined according to the method of Falhot et al. (1973).

— Apolipoproteins A and B were determined by single radial immunodiffusion technique according to the method of Cheung and Albers (1977) by plates supplied from Behring Institute.

— Lipoprotein electrophoresis was done to check the general pattern of lipoproteins as described by Winkelman et al. (1964).

— Total proteins were estimated using Biuret's method (Henry et al., 1957).

— Albumin was determined by bromocresol green binding according to the method of Doumas et al. (1971).

All results were analysed statistically by Student's t-test.

RESULTS

Table (1) shows that there is a small increase in the levels of total and free cholesterol, free fatty acids and triglycerides. This increase was not very significant. The values are within the normal range reported by other investigators.

Table (2) shows that total proteins, albumin and Apo-B showed no significant change. On the other hand Apo-A showed a significant increase.

DISCUSSION

Total cholesterol and triglycerides showed a slight increase during Ramadan fasting. This is in accordance to Fedail et al. (1982). This increase could be due to the high carbohydrate and sugar intake during nights of Ramadan. Sucrose is a well known factor to enhance lipogenesis (Eisenberg and Levy, 1975). It increases both cholesterol and triglycerides synthesis.

Egyptians as well as other Moslems are known to take a lot of sweety foods during Ramadan. Also, the intake of animal proteins and fat is usually increased during Ramadan. Both these food stuffs increase the level of blood cholesterol (Masoro, 1977). The increase in total cholesterol was not to the pathologic level.

HDL-cholesterol was significantly increased in this study. The value for HDL-cholesterol does not vary with age (Levy, 1981). Only few conditions are associated with increase in HDL-cholesterol. Exercise is an example. Nicotinic acid is a lipid lowering drug that regularly and uniformly increases the concentration of HDL-cholesterol while decreasing the concentration of LDL-cholesterol (Blum et al., 1977).

HDL, the good carriers of cholesterol are protective factors. It is highly significant to detect factors which may cause their increase. Ramadan Fasting is one of these factors as demonstrated in this study.

Apo-A proteins were significantly increased in this study during Ramadan. Yet, there was a slight decrease than those reported for Europeans, 134-187 mg/dl (Curry et al., 1976). Apo-A proteins were reported

to undergo no change during fasting (Fariah et al., 1975). Apo-A proteins were 1.36 g/l in the fasting group while after Ramadan they were only 1.18 g/l. Apo B protein level did not change significantly.

Serum FFA were not increased during fasting. Also, no ketone bodies were detected in serum in appreciable amounts. So, eating during the night in Ramadan was sufficient to build carbohydrates stores in the liver. Excessive lipolysis is not marked.

In this study, total proteins were 6.1 g/dl and albumin level 4.1 g/dl which are similar to the control group. Intermittent fasting has no detrimental effect on body proteins. The low level of serum albumin was reported before (Abou El Makarem et al., 1985) which reflects protein deficiency intake in Egyptians.

CONCLUSION

Blood lipids have not changed significantly during Ramadan. It is advisable not to consume much sucrose during the night, so the level of total cholesterol will not increase.

Values of blood constituents obtained during Ramadan are within normal range. Higher or lower values should be interpreted as pathologic.

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TABLE 1

EFFECT OF RAMADAN FASTING ON SERUM LIPIDS

	Mean ± S.D.		P value
	Control	Fasting	
Total cholesterol	172 ±38.4	193.7±34.3	0.05
HDL cholesterol	42.8± 5.8	62.7±11.4	0.002
HDL-c/total-c %	24.8± 3.3	32.4± 5.7	0.002
Free cholesterol	42.5± 6.6	51.9± 9.4	0.05
Free-c/total-c %	24.7± 3.8	26.8± 4.9	N.S.
FFA mmol/l	<1	<1	N.S.
Triglycerides	85.5±25.2	107 ±32.7	0.05

Total cholesterol, HDL cholesterol, free cholesterol and triglycerides are represented as mg/dl.
Results are the mean of 40 samples of blood from medical students, age 25.4 (20 - 35).

TABLE 2

EFFECT OF RAMADAN FASTING ON SERUM PROTEINS

		Mean ± SD		P value
		Control	Fasting	
Total proteins	g/dl	6.5 ± 0.6	6.1 ± 0.8	N.S.
Albumin	g/dl	4.3 ± 0.4	4.1 ± 0.4	N.S.
Apo-A	mg/dl	117.6 ±38.1	135.9 ±28.6	0.01
Apo-B	mg/dl	73.2 ±24.6	79.2 ±37.9	N.S.

HYPERPROLACTINEMIA AND POSTPARTUM ANOVULATION

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In all mammals, including man, lactation is a key link in the reproductive cycle. It serves the two equally important functions: covering the nutritional demands of the newborn and spacing out the birth interval.

The breast has two main physiological roles, and both are important for the survival of the young and for the preservation of the human species. The first one is the newborn's nourishment. The mother's milk not only provides energy but also contains specific (IgA antibodies), nonspecific (lysozyme, lactoferrin, lactoperoxydase, etc.), and antimicrobial factors, which are deficient in cow milk. The second physiological role is the contraceptive effect of breastfeeding. Breast stimulation, via a neuroendocrine reflex initiated by suckling, interferes with the hypothalamic control of ovulation. The duration of the postpartum amenorrhea and infertility is influenced mainly by the frequency and duration of breast stimulation by the child[1]

In women, serum levels of prolactin remain high during prolonged lactation. In Africa, the lactational hyperprolactinemia is of 1 to 2 years duration[2,4]. The most important factor controlling this hyperprolactinemia is frequency of suckling[5]. When mothers breastfeed their babies more than six times per day, their basal levels of serum prolactin remain at 1000 uU/ml for more than one year. When the frequency of breastfeeding is high enough, the serum levels of prolactin are permanently high. The progressive decline in breastfeeding practices[6], not adequately balanced by the use of effective methods of contraception is likely a decisive factor in the recent exponential increase of the human population. The purpose of this study is to review the data on the endocrine pattern related to hyperprolactinemia of long lasting lactation in nursing mothers.

Lactational hyperprolactinemia

Serum prolactin was measured in 54 single blood samples collected from nursing mothers of Kivu (Zaire). The method used for prolactin assay was radioimmunoassay as described by Badawi et al,[7], using the reagents distributed by the National Institute for Metabolism, Diabetes and Digestive and Kidney Diseases, the National Institute of Health, USA. The results were expressed in international units with reference to the 1st International Reference Preparation of human pituitary prolactin (National Institute of Biological Standards and Control, London).

The serum levels of prolactin progressively increase during pregnancy in women (fig. 1). At term, they are some 10 times higher than prior to gestation[8]. After delivery, the rapid disappearance of the large amounts of circulating progesterone and estrogens allows milk protein synthesis and full lactation by the influence of prolactin[9]. Serum prolactin levels decline progressively and, if the mother does not nurse the newborn, they return to pregnancy levels. In case of breastfeeds, each suckling cause a rapid rise in serum prolactin levels[10].

In mothers who nurse their children during two years or more, serum prolactin levels remain high (1000 uU/ml, for 15 to 18 months). This was first reported by Delvoye et al[2,4] for African mothers and confirmed later by other groups in Asia and South America[11]. The main factor controlling lactational hyperprolactinemia is the

frequency of breastfeeding. When the number of feeds per day is 6 or more, serum prolactin levels remain high for more than one year. When the number of feeds per day is below 6, serum prolactin returns to normal within 2 to 6 months[12]. The breastfeeding behavior varies from community to community[13]. Another factor influencing the lactational hyperprolactinemia is the nutritional status of the mother[14].

Lactational hyperprolactinemia has been also reported in other placental mammals as rats, dogs, pigs, cows and rhesus monkeys[15]. In all these species, too, it is associated with a period of lactational infertility. So, lactation serves the equally important function of spacing the intervals between successive births.

Long lasting lactation amenorrhea

The lactational hyperprolactinemia is associated with prolonged postpartum amenorrhea and anovulation[16]. There is a close association between the incidence of hyperprolactinemia and that of amenorrhea during the first two years of lactation in African mothers[3, 4, 11]. It is well documented that in breastfeeding mothers, the recurrence of menses is a bad marker of ovulation or restoration of fertility. During breastfeeding, the first cycles are often anovulatory or characterized by a luteal insufficiency.[11,17]

During the postpartum period, the time-course of the rate of hyperprolactinemia (serum prolactin level above 600 uU/ml) and that of the rate of amenorrhea are shown in fig 2. The two curves of hyperprolactinemia and amenorrhea are almost parallel and having the same pattern. The values decline during the first 6 postpartum months, then remain stable for 3 months. Afterwards, they decline progressively again until the end of the test period. The association of hyperprolactinemia and amenorrhea is statistically significant.

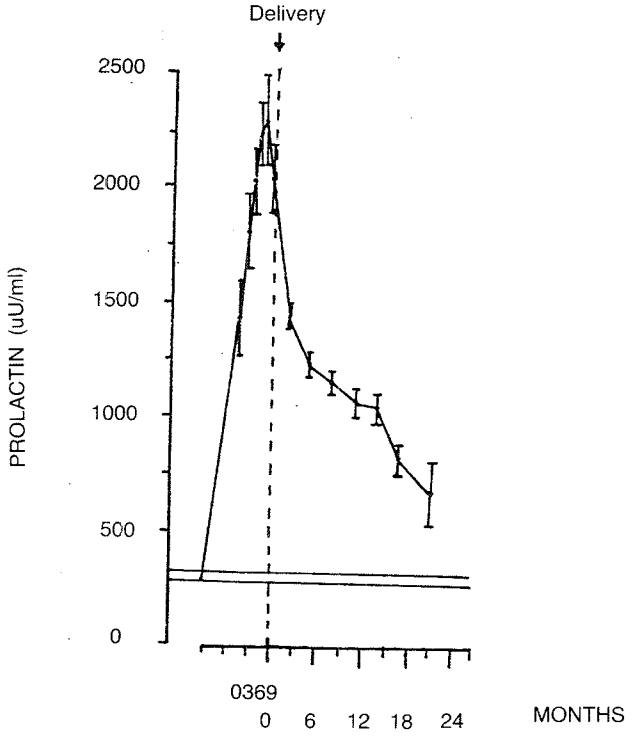

Fig. (1): Mean serum prolactin levels in uU MRC 71/222 per ml. (±SEM) in mothers from the Kivu (Zaire) during pregnancy and prolonged lactation. Mean ± SEM of serum prolactin levels in a group of non-pregnant and non-lactating women of the same region are represented by the two horizontal lines.

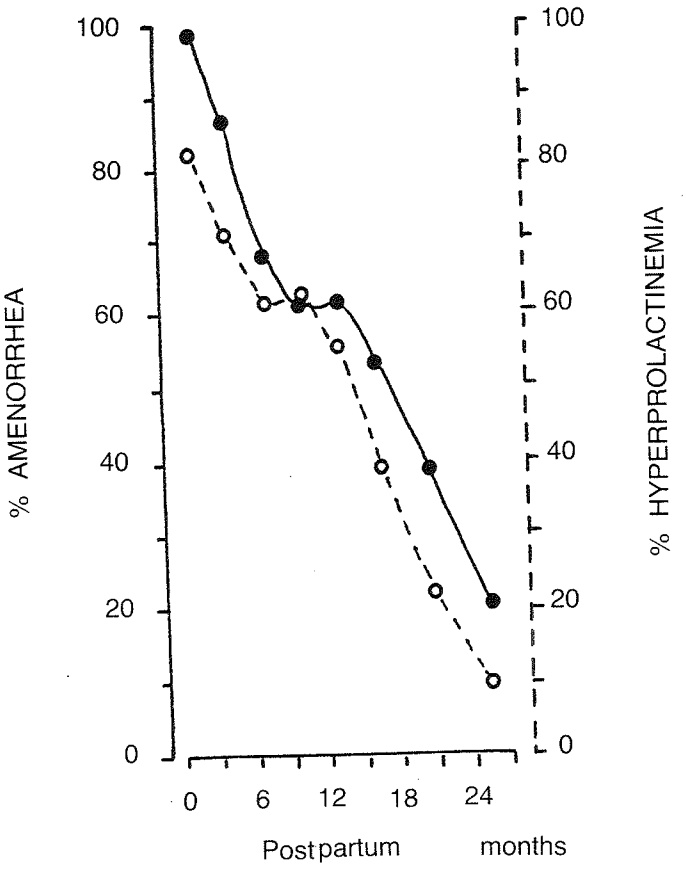

Fig. (2): Relationship between the occurrence of hyperprolactinemia (o....o) and amenorrhea (●....●) in a group of mothers from the Kivu (Zaire) according to the time of the post-partum.

CONCLUSION

Prolonged hyperprolactinemia is associated with long lasting lactation. It is the consequence of the high frequency of breastfeeding, more than 6 times per day. In breastfeeding, when the suckling frequency is high, provides a natural mechanism of birth spacing not only favorable to the survival of the child but also contributing to the control of population growth.

Lactational hyperprolactinemia plays a role in the prolonged post-partum anovulation and infertility. In addition to prolactin as the only factor controlling the lactational anovulation, suckling itself may exhibit a direct influence, via the central nervous system on the hypothalamic control of gondotrophin secretion.

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EFFECT OF ISLAMIC FASTING ON UROLOGICAL PATIENTS

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Dr. Mohamed Youssry and Dr. Abdelazim M. Abdelrahman
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In the name of GOD, THE MERCIFUL, the COMPASSIONATE

> *O BELIEVERS, PRESCRIBED FOR YOU IS THE FAST, EVEN AS IT WAS PRESCRIBED FOR THOSE THAT WERE BEFORE YOU-HAPPILY YOU WILL BE GODFEARING FOR DAYS NUMBERED; AND IF ANY OF YOU BE SICK, OR IF HE BE ON A JOURNEY, THEN A NUMBER OF OTHER DAYS; AND FOR THOSE WHO ARE ABLE TO FAST, A RANSOM BY FEEDING AN INDIGENT. YET BETTER IT IS FOR HIM WHO VOLUNTEERS GOOD, AND THAT YOU SHOULD FAST IS BETTER FOR YOU, IF YOU BUT KNOW.*
>
> *(S2:V183, 184)*

In Moslem communities, the Moslem physician is looked to as the 'Just' authority in questionnaire regarding Ramadan fasting which is a fundamental Islamic Rite.

Many disease conditions are quite evident indications for the postponement of fasting according to the Holy Quran, Surat Albaqara, Aya 183-184. An acute illness, a high fever or a debilitating disease are examples. However, the frequent puzzle are the chronic and the nondebilitating illness and the group of people searching for a licence to skip fasting. Many physicians easily recommend nonfasting while others are reluctant.

To all Moslem people and physicians, this work was carried out to identify some of the effects of the Moslems fasting on the body of normal volunteers and of patients who are stone formers and some with urinary tract infection. These are the commonest type of patients questioning fasting.

Ramadan fasting is day-time starvation and the abstination period varies from 9 to 19 hours according to the geographical situation of the place and the season in which Ramadan-the 9th lunar month comes.

REVIEW

Stone formation in the urinary tract is a complex problem. There are some hereditary and congenital metabolic factors as in cystine and uric acid lithiasis (Gram 1932; Goldstein; 1951). Endocrinal causes are exampled by hyperparathyroidism and calcium stones. Obstruction and/or infection in the urinary tract strongly favour stagnation of urine, change of pH, crystal deposition and stone formation. Urea is one of the preventive or dispersing colloids which work against stone formation.

There is geographic and climatic predisposition to urinary stones. Sutor and Wooly (1971), Rivera (1973), Toor (1974), and Elliot (1975) reported the highest incidence of calculi to be during the hot summer months.

Butt (1952) and Prince et al (1956) considered that the important factor is dehydration and urine concentration rather than the high atmospheric temperature. Blacklock (1969) reported that by increasing urinary output from 800-1200 ml daily through increased water intake caused a drop of 36% in incidence of urinary calculi in sailors. Finlayson et al (1974) suggested that a urine output of 3600 ml per day is necessary to be effective in stone prevention.

Diet has also some influence in calculosis. Thomas (1975) concluded that foods rich in calcium, oxalate and phosphate result in increased urinary excretion of these elements and probably contribute in formation of urinary calculi. Also purine-rich diets increase urinary excretion of uric acid and urate calculi. Hodgkinson (1976) and Peacock et al (1968) found that fasting overnight reduced the high serum and urinary calcium in hypercalciuric stone patients even to normal levels. Cathcard (1909) found that fasting could be associated with reduction in urinary uric acid. Margaret (1965) could detect rise in serum uric acid after starvation even for 1-2 days. Muzzan and Khaleque (1959) found no evidence of renal dysfunction during Ramadan fast and the fluid intake was adequate in all studied subjects.

Scott (1981) reported significant weight loss and reduction in the 24 hours urine volume in Ramadan fasting. He also found a rise in the total urine solutes (mainly urea) but usually after the third week of fasting.

Fedail et al (1982) found no change in body weight and serum uric acid but cholesterol rose and triglycerides dropped in Ramadan fasting. On the other hand, Yegin et al (1983) studied 100 normal Moslems of different ages fasting in Ramadan and compared their serum elements levels before Ramadan and in the last day of Ramadan. They found no change in serum proteins, lipids, cholesterol, uric acid and urea. But a significant rise was found in serum sodium and potassium. Blood sugar, free fatty acids and triglycerides were decreased.

Urinary tract infection: Acute urinary tract infection particularly in the kidney, prostate or testis is usually associated with marked systemic symptoms and requires postponement of the fasting.

The chronic infections are usually controversial but most patients and physicians do not advise non-fasting. If there is impairment of renal function the patient is frequently advised non-fasting particularly if the impairment is advanced and associated with vomiting and dehydration. However one wonders to see some patients in renal failure advised against fasting do much improve with Ramdadan fasting.

MATERIAL AND METHODS

150 persons were included in this study: 90 stone formers, 30 with chronic urinary tract infection and 30 normal controls.

All persons were in the age group from 21-56 years. All were subjected to history taking, clinical examination and radiograms of urinary tract (plain and I.V.U.) and urinalysis.

All were allowed to fast 10 days period in Ramadan in summer and also voluntary fasting in winter. Any new symptoms or signs or any change in an existing one was recorded in every patient or volunteer. They were subjected to urinary and serum examination for urea, creatinine, uric acid, calcium, sodium and potassium.

Blood samples were taken from an anticubital vein during non-fasting period, i.e. 3 hours after breakfast in Ramadan or after lunch in other times. The fasting samples were taken before breakfast in fastings. The serum was separated by centrifuging the blood samples.

Urine samples were collected during all hours of fasting and non-fasting separately.

The spectrophotometer and special kits were used to estimate serum and urine calcium, uric acid, urea and creatinine. A flame photometer was used to estimate serum sodium and potassium.

Statistical analysis of the results was made based upon Schwarz formula.

RESULTS

Clinical evaluation: The patients of stone group were 90, of them 65 males and 25 females, their age ranged between 21 and 56 years. The 30 with chronic urinary tract infection included 18 females and 12 males, aged between 20 and 54 years. The 30 volunteers were 25 males and 5 females, aged between 20 and 45 years.

All persons included in this study were leading an office occupation with few sportsmen and manual workers.

The symptoms and signs during the fasting period in both patients and volunteers were the same (Table I)

Table I

Groups	Headache	General Weakness	Renal Colic	Burning Micturitition
Volunteers (30)	**12**	**4**	**0**	**2**
Stone patients (90)	**26**	**15**	**4**	**6**
Infected patients (30)	**11**	**6**	**1**	**3**

The headache is a common symptom in fasting particularly during the early days of Ramadan. A general sensation of weakness is also common among fasters at the end of daytime. Two patients with stones experienced an attack of renal colic and painful micturition during fasting and they were accustomed as well to similar episodes during non-fasting. The group of urinary tract infection had also bouts of painful micturition usually late in the day of fasting.

The vital signs in all patients and volunteers were within normal limits both during the fasting and non-fasting periods.

Urine volume: There was reduction in the urine volume and increase in the specific gravity in the fasting period in all groups and also a significant drop in the 24 hours urine volume and rise in the specific gravity particularly during summer.

Urinalysis during the non-fasting and fasting periods were also not different in all groups. There was increase in the incidence of oxaluria among all during the fasting probably related to the type of diet during the non-fasting period (Table II)

Table II : URINALYSIS

Groups		Oxaluria	Phosphate	RBC (H.P.F.) <10	RBC (H.P.F.) >10	WBC (H.P.F.) <10	WBC (H.P.F.) >10
Non-fasting	Volunteers (30)	2	—	29	1	28	2
	Stones (90)	17	5	70	20	75	15
	Infection (30)	1	4	14	16	5	25
Fasting	Volunteers (30)	3	1	29	1	28	2
	Stones (90)	20	4	69	21	74	16
	Infection (30)	2	3	12	18	4	26

The Electrolytes: In the group with urinary tract infection, the number of pus cells and bacterial counts in the urine samples both during normal feeding and fasting showed no significant change.

The serum calcium (normal 8.9-10.7mg%) did not show statistically significant changes in all groups of tested persons in summer or winter during fasting. However, the urine calcium content (normal 50-300 mg/24 hours) revealed a statistically slight significant reduction in all groups in all seasons.

As regards sodium and potassium, fasting in both seasons did not produce significant changes in the serum Na or K. Also there was statistically insignificant increase in the mean value of urinary Na and K in the normals. In the infected group and in the stone formers the urinary Na and K showed a highly significant increase.

For uric acid, fasting did not change the serum values in all groups, while it led to statistically insignificant reduction in the urinary uric acid. There was insignificant increase by fasting in the mean levels of both blood and urine urea in all groups.

Fasting led to insignificant increase in serum creatinine in all groups. The urine creatinine showed a highly significant increase in the fasting normal volunteers while the increase was significant in stone formers and no change in the group with urinary tract infectiion. The results are summarised in Fig. 1.

Fig. 1: SUMMARY OF RESULTS

	Calcium		Uric Acid		Sodium		Potassium		Urea		Creatinine	
	N	Pts	N	Pts	N	Pts	N	Pts	N	Pts	N	Pts
SERUM												
URINE												

Statistically insignificant change
Statistically slight significant decrease
Statistically high significant increase

DISCUSSION

The Moslems rite of fasting during Ramadan and in other days of the year has been frequently questioned as advisable or to be avoided by the urological patient, particularly stone formers and those with urinary tract infection.

In Moslems fasting there is abstinence from food and drink for about 9-19 hours, then return to natural intake. So any reported changes in the body during fasting are expected to be temporary.

During the fasting period we found a highly significant decrease in the urine volume in all groups of people studied. This depends upon the osmoreceptors and antidiuretic hormone release which regulate the urine excretion according to the water intake.

The urine specific gravity increased significantly during fasting period. Scott (1981) ascribed the increase in specific gravity to increased excretion of urea which forms about 80% of urinary solutes. Urea being a dispersing colloid can help in non-precipitation of urinary salts which form urinary calculi.

Serum calcium levels showed no change but calcium in urine was slightly, significantly, decreased. Peacock et al (1968) found that overnight fasting in hypercalciuricstone formers depresses serum and urine calcium level to normal range.

Uric acid in the serum and urine did not change by fasting. This is in accordance with the findings of Fedail et al (1982).

Serum sodium and potassium did not alter by fasting. In the urine, their level showed an increase which was significant in the group of patients with calculi and urinary tract infection. This was, however, temporary and the levels returned to normal during non-fasting. Garnett et al (1973) also found temporary natriuresis with starvation. Yegin et al (1983) reported a rise in serum sodium and potassium in the last days of Ramadan in comparison to the level in the first days. The rise in urinary sodium is physiologically inhibitory to calcium cyrstallization in the urine, hence it may have an inhibitory effect on stone formation.

Urine creatinine was raised significantly only in the control fasting group. This was temporary. The kindey function in these patients was not affected and the creatinine is basically of endogenous origin (Wallin 1979). Hence, this may be due to a factor yet unexplainable.

This study shows that Moslems (Ramadan) fasting has no deleterious effect on the kindey or urinary tract function neither in normal controls nor in the studied group of patients with calculi or chronic infection. The results of the carried analysis although suggesting a rise in urinary crystals (oxalate-urate), yet the increase in urinary urea, sodium and potassium is inhibitory to stone formation.

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SCIENTIFIC EVALUATION OF SLAUGHTER AND STUNNING METHODS

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In an ideal situation, the stunning method should render the animal unconscious similar to anaesthesia with no alteration of any physiological functions. However, since none of the utilised methods of stunning fulfill this requirement, it is important to evaluate the approved methods in order to determine which of the approved methods is the most acceptable; also, this paper will be concerned with the influence of different stunning methods on the meat quality.

It has been reported that many biochemical and physiological changes are triggered at stunning and exsanguination. As the tissues lose their blood supply and become anoxic the tissue cannot resynthesise ATP via the oxidative phosphorylation mechanism. Continuous hydrolysis of ATP leads to the accumulation of inorganic phosphate which stimulates the metabolism of glycogen to lactic acid. Rates of postmortem glycolysis can be accelerated and the muscle pH values can go down to less than 5.8 by antemortem treatment such as severe struggling.

All of the approved stunning methods induce severe struggling during or after stunning.

Captive-bolt devices destroy the higher brain centres due to the concussion of the blow and the direct destruction caused by the bolt if a penetrating device is used. The direct stimulation of the higher brain centres causes the animal to fall and lie trembling for three to ten seconds at which time the animal begins to kick violently for approximately 30 seconds or until exsanguination is complete. Therefore it is often difficult and hazardous to shackle and stick swine stunned by this method.

The responses to electrical stunning are similar to those of captive-bolt stunning in that the muscles are in a state of tetanus while the current is being applied. The animal falls when the current flow ceases and lies trembling for a few seconds and then the legs begin to move in a somewhat coordinated running manner. The duration and intensity of the struggling appears to be related to the voltage, amperage and duration of stunning. However, if the energy used to stun the animal is increased to the point that struggling is reduced, it seems we then create problems in the form of muscle hemorrhages and broken backs in the carcasses.

From the descriptions of responses to mechanical and electrical stunning, one might expect that little struggling would be associated with the use of carbon dioxide, since there would be no direct neural stimulation in the CO_2 tunnel. However, animals often resist entering the tunnel and react violently to the CO_2. The usual response is that the animals become excited, throw their heads backward and collapse approximately 15 secnds after encountering the 70 percent CO_2 atmosphere. Heart and respiratory functions are not impaired and the animal will then lie quietly for two to three minutes during which time it can be bled safely and efficiently.

Recent research by Althen et al (1975) and Ono et al (1976) examined the stress of stunning methods on catecholamine release and cyclic-AMP production. These studies were designed to determine if stunning

methods could alter catecholamine levels and to determine if the effects of the catecholamines were being mediated through cyclic-AMP to stimulate glycogenolysis. Their results suggest that mechanical methods of stunning stimulate the release of epinephrine and norepinephrine and induce a corresponding increase in muscle cyclic-AMP. The authors compared the responses to electrical stunning and stunning by gunshot to responses of animals that received no preslaughter immobilisation and recorded increases in epinephrine and norepinephrine of 600 and 1100 times respectively over resting or prestunning levels. There was also a five-fold increase in cyclic-AMP levels due to stunning by gunshot. After stunning by gunshot the epinephrine levels were eight times those in electrically-stunned animals and 28 times those of non-stunned animals. Norepinephrine levels among animals stunned by gunshot were increased 42 times over those electrically stunned and 260 times over those receiving no stunning. Cyclic AMP levels among non-stunned and electrically-stunned animals were not different and were approximately 60% of those for animals stunned by gunshot. Since stunning by gunshot is analogous to the use of penetrating captive-bolt devices, and since the levels of catecholamines and cyclic-AMP were significantly greater in those animals when compared to animals stunned electrically, the authors concluded that electrical stunning was less stressful to animals than captive-bolt stunning.

Sybesma and Groen (1970) compared responses to CO_2 immobilisation using a commercial tunnel facility, 70 volt electrical stunning and 70 volt stunning after animals had passed through the tunnel without CO_2 present. The animals that passed through the empty tunnel and were stunned by the 70 volt treatment had the most rapid rate of post-mortem metabolism whereas those stunned by the 70 volt treatment without exposure to the tunnel showed the slowest rate of post-mortem glycolysis. These authors concluded that the stress of getting the animals into the CO_2 tunnel accelerated the rate of post-mortem glycolysis. Animals receiving only the CO_2 treatment had a rapid rate of post-mortem glycolysis similar to those receiving the tunnel stress plus the 70 volt treatment. The use of CO_2 for immobilisation has also been linked to reduced bleed-out of carcasses (Leest et al, 1970) although this is apparently of importance with respect to the adverse effect CO_2 stunning might have on post-mortem glycolysis rate.

In a rather comprehensive study, Leest et al (1970) utilised 600 animals in a commercial slaughter facility to compare the use of CO_2, 70 volt A.C. and 300 volt A.C. as stunning methods and their effect on meat quality. No differences in responses were noted between the 70 and 300 volt A.C. treatments. However, the animals immobilised with CO_2 and shackled prior to exsanguination had significantly lower blood and muscle pH at death and lower muscle pH at 35 minutes postmortem. Muscle rigor value was also higher at 35 minutes postmortem as were lactic acid levels at death and at 35 minutes. Muscle ATP levels were lower at 35 minutes postmortem and haemoglobin concentration, an index of residual blood, was higher among carcasses from animals immobilised with CO_2. However, the incidence of shoulder haemorrhages was higher among animals stunned by the 70 volt A.C. treatment. The authors attributed the lower blood and muscle pH and increased muscle lactate levels of the CO_2-treated animals to the anoxia that resulted from inhalation of the Co_2-air mixture. The anoxia from CO_2 treatment was also believed to contribute to the more rapid depletion of muscle ATP levels noted at 35 minutes post mortem.

Overstreet et al (1975) compared responses of animals to restraint and stunning with captive-bolt pistol, CO_2, 90 volt A.C. and 290 volt A.C. to determine the effect of each on post-mortem glycolysis. Animals that were slaughtered without restraining or stunning had the slowest rate of post-mortem glycolysis, which was indicated by higher levels of muscle ATP and creatine phosphate, higher muscle pH and lower muscle lactic acid concentrations at one hour postmortem. Animals subjected to CO_2 immobilisation had the lowest blood pH and the highest blood CO_2 values at death. The greatest decrease in muscle ATP levels represented by the difference between levels in biopsies taken 24 hours prior to slaughter and levels found at one hour post-mortem was found among animals stunned by the captive-bolt pistol. The authors were unable to find any

consistently significant differences among responses to the 90 volt, 290 volt or CO_2 stunning systems and suggested that the selection of a given method could be based on personal choice and available facilities. However, it was suggested that the use of the captive-bolt pistol should be discouraged in research situations when muscle glycolysis is to be studied. Also, the act of simply restraining the animals without stunning resulted in a response equal to that of the stunning methods in terms of accelerating post-mortem glycolysis, which emphasises the fact that animals must not be stressed prior to slaughter.

If we accept that electrical stunning is the least stressful of the approved methods which makes it the preferred method of stunning, we must be aware that there are two quality problems associated with its use. As a result of electrical stunning, a significant number of animal carcasses contain broken vertebrae and muscle haemorrhages. Muscle haemorrhages ranging in size from one to five millimetres are quite common and have been noted as early as 1929 (Ducksbury and Anthony). A report in 1932 suggested that these haemorrhages may be due to the rise in blood pressure that occurs during electrical stunning (Clark and Tweed, 1932). Perhaps the best evidence that the changes in blood pressure were associated with muscle haemorrhages were provided by Shaw et al (1971), who were able to produce similar responses in electrically-stunned animals. These authors found that pretreatment with drugs that caused increased capillary blood pressure prior to stunning also caused an increase in the incidence of haemorrhages was reduced when the animals were pretreated with drugs that lowered the average capillary blood pressure.

As a result of the many studies between 1932 and 1970 it was found that the incidence of muscle haemorrhages could be reduced by using higher stunning voltages (300 volts vs 70-90 volts) with shorter application times (Leest et al, 1970); a shorter interval between cessation of current flow and exsanguination (Mandrup, 1964); and the use of an alternating current with a square or trapezoid waveform instead of the normal sine wave (Szucs et al 1963). More recently, Hatton and Ratcliffe (1973) reported that the use of high frequency stunning (1300 Hz) reduced the incidence of haemorrhages by aproximately 80 percent when compared to the incidence in animals stunned with low voltage, low frequency current.

McLoughlin (1971) examined the effects of neural stimulation on post-mortem changes and found that muscle ATP concentrations declined to their minimum value by two hours post-mortem in animals slaughtered normally. However, little depletion of ATP occurred until three hours post-mortem in muscle from animals anaesthetised prior to exsanguination. ATP concentrations in muscle from the anaesthetised animals then declined slowly during the period from three to six hours post-mortem. This slower rate of ATP depletion would not stimulate anaerobic glycolysis to the same extent found in animals slaughtered normally and emphasises the value of inducing true anaesthesia prior to slaughter.

In an attempt to develop a more ideal type of immobilisation method, Cordray et al (1976) compared animal responses to CO_2 and nitrous oxide. Nitrous oxide has the same density as CO_2 and therefore could be used in existing equipment and has the distinction of being a general anaesthetic. The treatments consisted of inhalation of 100% nitrous oxide or a mixture of 75% CO_2 and 25% air. No significant treatment differences were noted in the rate of post-mortem glycolysis although subjective evaluation suggested that those animals immobilised with nitrous oxide reacted less violently than those receiving CO_2. As in the study by Overstreet et al (1975), all animals were restrained in a head gate chute while receiving the immobilisation gas and the stress of restraint may have masked beneficial aspects of either treatment. Although the principle of using a general anaesthetic is sound, the use of nitrous oxide could be questioned since it does not have the property of being a good muscle relaxant. However, it is doubtful that other gaseous general anaesthetics will be of value since the remaining ones are either highly explosive, highly expensive and/or would be expected to leave high levels of residual activity in the carcass thereby making acceptance by the Inspection system virtually impossible.

In conclusion, the literature suggests: 1) That captive-bolt stunning should be discouraged in terms of its adverse effect on meat quality. 2) The use of CO_2 appears to be more stressful than electrical stunning. 3) High voltage electrical stunning is superior to the use of low voltage stunning and is likely the best of the methods used today provided the animals are exsanguinated immediately after cessation of stunning. 4) There also appears to be an advantage in the use of high frequency electrical stunning to reduce the incidence of muscle haemorrhages.

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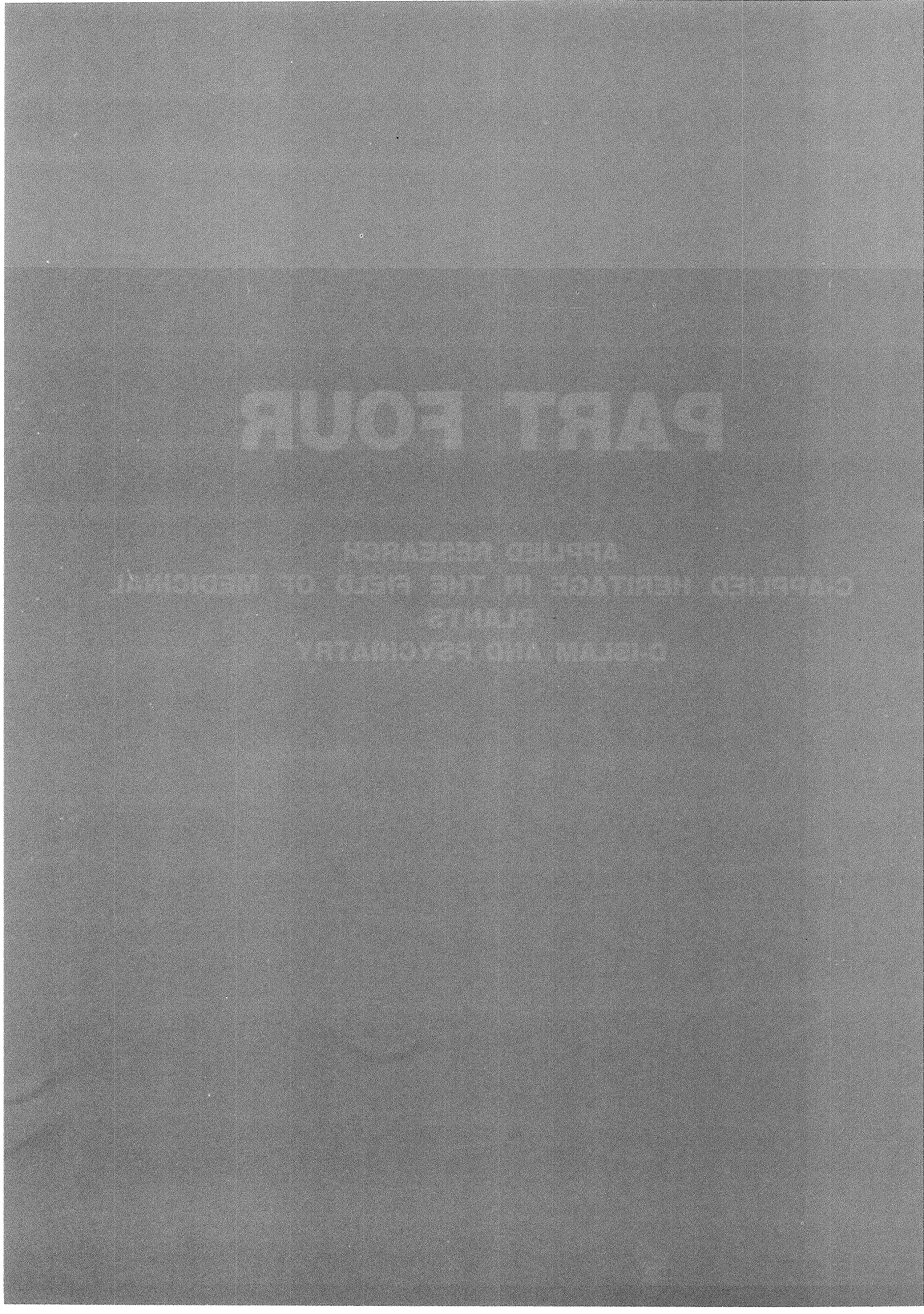
PART FOUR

APPLIED RESEARCH
C-APPLIED HERITAGE IN THE FIELD OF MEDICINAL PLANTS
D-ISLAM AND PSYCHIATRY



CHAPTER I
PLENARY LECTURE

REPORT ON THE FIRST SESSION

This session was chaired by Prof. Dr. Atta-ur-Rahman and moderated by Dr. Abdul Fattah Shawki. The Co-chairman Prof. Dr. S.I. Ahmed was not present.

The plenary lecture was delivered by H.E. Dr. Mohd. Al-Ahmadi Abu Al-Noor entitled "Duties and rights of the physicians in Islam" and the main lecture by Dr. Ahmed El-Kadi on the "Effect of the black seed on immunity". The other speakers were Prof. Dr. Mohammad Sabir, Dr. Saleh Al-Jaraiwi, Hakim Rasheed Ashraf Nadvi and Dr. Inamul Haq who respectively spoke an "Pharmacological evaluation of the anti-inflammatory activity of certain medicinal plants", "Preliminary clinical evaluation of certain herbal remedies in the treatment of vitiligo", "The academic and scientific nature and value of Islamic medicine" and "Quality control of Islamic medicine". One scheduled paper by Prof. Dr. H. Wagner entitled "Liver drugs of traditional oriental medicine" was not presented.

At the end of lectures, the chairman invited questions, comments and remarks from the audience. Over 150 scholars were present. The delegates took part in discussion, especially on the paper of Dr. Mohd. Al-Ahmadi Abu Noor, and came to conclusion that the physicians (of Islamic medicine) should be fully conversant with the Holy Quran, Ahadith and ancient classical literature of Tibb and they should follow the principles as mentioned therein, so that the characteristics of service to mankind be developed among them.

-Editors

Part Four: *Applied Research: C-Applied Heritage in the field of Medicinal Plants.*

CHAPTER II

C - APPLIED HERITAGE IN THE FIELD OF MEDICINAL PLANTS

MAIN LECTURE:

1. EFFECT OF *NIGELLA SATIVA* (THE BLACK SEED) ON IMMUNITY
   Dr. Ahmed El-Kadi, *et. al.*

PAPERS PRESENTED:

2. PHARMACOLOGICAL EVALUATION OF THE ANTI-INFLAMMATORY ACTIVITY OF CERTAIN MEDICINAL PLANTS
   Dr. Ahmed R. El-Gindy, *et. al.*
3. PRELIMINARY CLINICAL EVALUATION OF CERTAIN HERBAL REMEDIES IN THE TREATMENT OF VITILIGO
   Dr. Saleh Al-Jeraiwi, *et. al.*
4. THE ACADEMIC AND SCIENTIFIC NATURE AND VALUE OF ISLAMIC MEDICINE
   Hk. Rasheed Ashraf Nadvi
5. QUALITY CONTROL OF ISLAMIC MEDICINE
   Dr. Inamul Haq
6. SUMMARY OF DISCUSSION

EFFECT OF *NIGELLA SATIVA* (THE BLACK SEED) ON IMMUNITY

Dr. Ahmed Elkadi and Dr. Osama Kandil

U.S.A.

Our interest in *Nigella sativa* (the Black Seed) was initiated by the authentic saying of Prophet Muhammad, (ﷺ) :

«في الحبة السوداء شفاء من كل داءٍ إلا السام»

"In the Black seed there is healing for every illness except death"[1] by Al-Bukhari

Nigella sativa belongs to the family of Ranunculaceae. Its seed also known as black seed, black caraway, black cumin, and by several other names, has been in use in many Middle Eastern and Far Eastern countries as a natural remedy for over 2000 years. In Egypt it is called "Habbat-ul-Barakah" which means the seed of blessing.

The seed is black and minute possessing an aromatic odor and taste and is frequently added to bread as a flavoring agent. As a natural remedy people take it minced by itself or mixed with honey, or use its oil, either as a promotor of good health or for the treatment of a variety of ailments.

In Unani Medicine it is used as detergent, digestive, carminative, stomachic, laxative, antibilious, anthelmentic, diuretic, lithontriptic, emmenagogue, galactogogue, stimulant, antiphlegmatic, expectorant and local anesthetic. Dawood Al-Antaki (in his famous ancient prescription book) identified the seed and used its oil in the treatment of bronchial diseases[2]. Mahfouz and El-Dakhakh in 1959 isolated the cyrstaline active principle "Nigellone" with the chemical formula $C_{18}H_{22}0_4$ from the oil of *Nigella sativa* seeds[3]. They documented the ability of Nigellone to prevent histamine-induced bronchospasm in the experimental animal.[4] Clinical studies have also shown a beneficial effect of Nigellone in the treatment of patients with bronchial asthma[4].In the experimental animal,[4] Nigellone was found to be free of any irritant or toxic effects whatsoever, even when injected in large doses[2]. Other studies showed that the extracts of *Nigella sativa* seeds have a marked choleretic effect causing an increase of bile flow,[5] an antibacterial effect,[6] and a hypotensive effect.[7]

In view of the multitude of uses of *Nigella sativa* where its effectiveness was documented, and primarily because of the above listed Prophet's saying indicating that there is healing for every illness in the Black Seed, we suspected that the Black Seed may have some stimulating effect on the immune system of the human body. The purpose of this study is to evaluate such an effect if any is present.

What is the immune system?

We may compare the immune system to an army and a police force which protects the body against invading harmful matters, microorganisms, and cancer cells. It is the body's own defence against infections and cancers. The job is carried out by specialized cells such as the various types of T-lymphocytes, B-lymphocytes, and Macro-phages; and several bio-chemical compounds - proteins - produced by these specialized cells. The T cells are the lymphocytes which had special training in the thymus gland. There are three specialities among the T cells: The helper T cells (or T_4) which activate the immune battle and give instructions to other cells telling them what to do; the killer T cells (or Natural Killer cell) which kill the invading

enemy units; and the suppressor T cell (or T_8) which give signal to the other cells to end the battle. In normal health the number of the helper T cells is twice the number of the suppressor T cells. The bio-chemical compounds include Interleukin 1 and 2 (IL-1, IL-2), Tumor Necrosis Factor (TNF), Gamma Interferon (I-F), B-Cell Growth Factor (BCGF), B Cell Differential Factor (BCDF), and a huge number of Antibodies. The battle starts when the macro-phages (the big eaters) meet the enemy units, be it a virus, a micro-organism, or a cancer cell. The macro-phages consume some of the enemy units, seize their antigens and display them on their own surfaces. Among millions of helper T cells circulating in the blood stream, a select few are programmed to read that antigen. These helper T cells couple with the Marco-phages. We may call this the vital union which starts the activation process of the T cells. The Macro-phages secrete the lymphokine Interlenkin 1 (IL-1) which activates the Helper T cell. IL-1 also stimulates the brain to raise the body temperature causing fever which enhances the activity of the immune cells. The activated helper T cell produces another lymphokine, Interleukin 2 (IL-2) which activates other helper and killer T cells to grow and multiply. The activated helper T cells also produce the lymphokine B Cell Growth Factor (BCGF) which causes the B Cells to multiply. As the number of B Cells increases the helper T cells produce another lymphokine, the B Cell Differention Factor (BCDF) which instructs some of the B cells to stop replicating and start producing antibodies. The helper T cells also produce a lymphokine called Gamma Interferon (IF) which has multiple effects. Like IL-2 it helps activate Killer T cells enabling them to attack the invading enemy units. Like BCDF, Gamma Interferon increases the ability of B cells to produce antibodies. It also affects macrophages, keeping them at the site of the battle and helping them digest the cells they have consumed.

Then the Killer T cells, which were recruited and activated by the Helper T cells, start performing their specialized job which is killing cells of the body that have been invaded by foreign organisms, as well as cells that have become concerous. The antibodies which were produced by the B cells rush to the battle field where they either neutralize the enemy units or tag them for attack by other cells or chemicals.

When the enemy units are conquered and controlled, the Suppressor T cells halt the entire range of immune responses preventing them from going out of control. They slow down or stop the activities of the B cells and other T cells, Memory T and B cells which are defense cells generated during the initial phase of the battle, are left in the blood and lymphatic system where they will circulate for years to enable the body to respond more quickly to subsequent attacks bythe same enemy.

Studies to evaluate the immune system

Among numerous studies available to evaluate the immune system we currently perform the following studies and feel that they offer adequate indication of the effectiveness of the immune system of a given person:

The total count of B cells and T cells, the count of the subgroups of Helper T cells (T4) and Suppressor T cells (T8), the ratio between T4 and T8, the Natural Killer cell activity, and the various Immune Globulins representing the antibodies. We may add additional functional studies to our immune profile testing in the future.

For better understanding of the results of the Natural Killer cell activity studies it should be explained that the test is done by incubating isolated Effector cells, which are the Natural Killer cells of the person to be tested, with Target cells, which are cancer cells grown in the laboratory in a tissue culture medium. The Target cells are labelled with radio-active chromium 51 (^{51}Cr) prior to the incubation with the Effector cells. The mixing of Effector and Target cells is done in 3 different dilutions, or Effector: Target ratio (ET ratio) of 10:1, 50:1, and 100:1. The degree of cytotoxic activity of the Natural Killer cells, which corresponds to the degree of lysis (or death) of the cancer cells is determined by measuring the amount of released radio-active material in the

supernatant fluid with a Gamma Counter. A different activity level is measured for each of the three dilutions, or Effectors to Target ratios.

METHODS AND MATERIAL

Apparently healthy volunteers were randomized into 2 groups. One group received one gram of ground *Nigella sativa* seeds twice a day, while the other group received activated charcoal powder as a placebo. The ground Nigella seeds as well as the placebo were packed in identical capsules. The identity of the capsules was known only to one of the investigators. The volunteers did not know which kind they were taking nor did the other investigator who was incharge of performing and interpreting the immune studies. The code was not broken until all the results were available for every volunteer. The results which are presented in this report are those of 27 volunteers, 16 males and 11 females, ranging in age from 10 to 60 years, with an average age of 33 years. Among the 27 volunteers there were 22 Muslims and 5 Non-muslims. Eleven of the 27 took real Nigella, 12 took Placebo, and 4 volunteers took Nothing. Two of the four who took Nothing were supposed be in the Nigella group, while the other two were supposed to be in the Placebo group. These four did not take their capsules for various personal reasons. The groups of Nigella and Placebo were reasonably well matched.

The initial protocol had one hundred volunteers on it for the study. The results which were indicated in the earlier abstract were the preliminary results of the first 10 volunteers. For some technical and financial reasons the studies could not be completed in time for this presentation except for the 27 volunteers which are the subject of this report. All volunteers had their immune profile evaluated before the study and 6 weeks after the study was started. The immune profile included a complete B cell and T cell count including the T cell subgroups of Helper T cells (T4) and Suppressor T cells (T8). It also included the Natural Killer (NK) cell functional activity assay, and the measurement of the Immune Globulins I_gA, I_gG, and I_gM. The two main indicators for the effectiveness of the immune system would be the T4: T8 ratio, and the NK cell functional activity level. An increase or enhancement of either one is considered an improvement while a reduction or decline is considered a deterioration.

RESULTS

In the Nigella group there were varying degrees of enhancement of both the T4: T8 ratio as well as the NK cell activity level in the majority of subjects while a few had a decline. The net results indicated an improvement of the T4: T8 ratio from 1.19 to 1.85 which is a 55% improvement (Fig. 1 & 2). The net enhancement of NK cell activity was 24% at 10:1 ET ratio, 10% at 50:1 ET ratio and 42% at 100:1 ET ratio (Fig. 3). The Immune globulin levels had an average decrease of 32.5% for I_gA, 12.6% for I_gG, and 29.4% for I_gM.

In the activated charcoal group the T4: T8 ratio showed an average decrease form 1.27 to 0.95, which is a deterioration of 25%. However, all subjects taking the charcoal showed varying degrees of NK cell activity with an average improvement of 63% at 10:1 ET ratio, 56% at 50:1 ET ratio, and 66% at 100:1 ET ratio (Fig. 4). The Immune globulins showed an average decrease of 27.4% for I_gA, 19.4% for I_gG and a minimal increase of 1.4% for I_gM.

In the third group who took Nothing there was an average decrease of T4: T8 ratio from 1.1 to 0.97 which is a 12% deterioration. There was also a decline in the NK cell activity at all dilution levels in all subjects averaging 32% for 10:1 ET ratio, 23% for 50:1 ET ratio, and 19% for 100:1 ET ratio. The Immune globulins in this group showed an average decrease of 8.9% for I_gA, and 3.8% for I_gG, but an average increase of 90% for I_gM.

Reported side effects included one volunteer in the Nigella group reporting that he was not losing his hair as he used to. Another one in the same group reported recurrent indigestion necessitating discontinuation of

the Nigella. In the charcoal group one reported that her finger nails became much stronger. No other significant side effects were reported.

DISCUSSION

In addition to the confirmation of a positive stimulating effect of *Nigella sativa* (the Black Seed) on the immune system, the results of this study gave us several surprising but very useful pieces of information. The biggest surprise was the significant and real enhancement found in the charcoal group. A positive placebo effect might be expected in up to 30% of subjects, and to a degree of improvement of up to 30%. In this group all the subjects had improvement, and to a level much higher than would be expected from a placebo. Even more impressive was the fact that all of the subjects who took nothing had a significant decline. This shows two things: First that activated charcoal was the wrong choice as a placebo. Second, and this was the very pleasant surprise, that charcoal caused a significant improvement of the immune functions. The puzzling question remained, how did it do it? Charcoal is not supposed to be absorbed from the intestimal tract, and therefore it was not expected to have any direct effect on the immune system. This continues to be true. The effect is apparently an indirect one through a different mechanism which we did not consider initially. Activated charcoal has the ability to absorb toxic chemicals in the digestive tract and is often given by mouth as a treatment following ingestion of toxic material. It is frequently used in water filters to absorb chlorine and other chemical impurities in the water. Apparently what happened in our charcoal group the charcoal absorbed all toxic chemicals contained in the ingested food and drinks, and left only the clean pure natural nutrients to be absorbed through the intestinal tract. But were there any toxic chemicals in the food and drinks ingested by these volunteers? Apparently, Yes! Nutritionists and members of the so called "Health Movement" have been claiming for years that all the artificial chemicals added to the food and drinks are harmful and may be responsible for suppressing our immune system leading to increase of cancers, infections, and other diseases; and should therefore be avoided. These artificial chemicals are in the form of a huge number of preservatives, artificial colours, artificial flavours, bleaching agents, many food additives, industrial pollutants to water, air, and soil which may again affect drinking water or plants growing from contaminated soil, and the list goes on and on. Once these harmful toxic chemicals were eliminated from the food and drinks by means of the charcoal, their suppressive effect was lifted away from the immune system, and the immune cells were allowed to grow and flourish without restriction. These facts about pure natural nutrients and their effect on the immune system have been known for years but were mainly based on logic and indirect evidence. To my knowledge, this is the first time that these facts are confirmed in such a direct and clear way as it happened accidentally in our study.

Another interesting finding was the fact that these so called "healthy volunteers" were not really that healthy. The majority of them had a somewhat impaired immune function. We tried to see if those with impaired immunity had something in common and indeed they did.The majority of these volunteers worked at or belonged to families of those who worked at the Akbar clinic and its afiliated projects. All of these are under a considerable degree of stress, mostly financial, and otherwise too. In the Nigella group we found that the few who had a decline of the NK cell functions had a particularly high level of stress during the period of the study due to sickness in the family or some other hardship, making their share of stress higher than the average member of the group. The stress situation to which most of the participants of the study were subjected would also explain the fact that all volunteers who took nothing had deterioration of their immune functions. Of course, there is nothing new in the fact that stress impairs the immune functions. This has been proven in many other studies. The significance of this finding in our study is that the actual real improvement caused by the Nigella or the charcoal is higher than the given figures. Because, if it were not for the stimulating agent (be it the Nigella as the pure natural nutrients), the decline would not be only down to the Zero level, but it

would have gone lower to the level of those who took Nothing. Therefore, one could probably add the decline figures in the "Nothing" group (i.e. 32%, 23%, and 19%) to the enhancement figures in the other groups. This would make the real net enhancement figures for Nigella close to 56%, 33%, and 61% in the various dilutions.

Other factors to be considered while reviewing these results are: First is the fact that we have tested only one dosage of Nigella, i.e. one gram twice a day. A higher dosage may have a more potent effect. This has to be determined in future studies. Second is the fact that these volunteers, although under stress, were still relatively healthy and free of any cancer or other immune deficiency disorder. The improvement in such persons is expected to be limited anyway since they were not that for from normal to start with. If Nigella or the pure nutrients were tested in subjects who are really bad, the improvement would possibly be more dramatic. In our advanced cancer patients receiving our multimodality immunotherapy program (in which Nigella is one of several components) we see enhancements of NK cell activity not in the range of 50-60% but in the range of 200-300%. We plan to have some controlled studies on isolated Nigella in some of these patients in the near future, insha'allah.

CONCLUSIONS

1. *Nigella sativa* seeds (the Black Seed) taken by mouth in a dosage of one gram twice a day have an enhancing effect on the immune functions, manifested in improved helper suppressor T cell ratio, and an improved natural killer cell functional activity.
2. The use of activated charcoal by mouth resulted in improved natural killer cell functional activity, most likely by eliminating the toxic chemicals from the ingested food and drinks, and allowing only the pure natural nutrients to be absorbed through the intestinal tract. The pure natural nutrients were thus able to exert their beneficial and immune enhancing effect.
3. Stress has a definite immune suppressive effect.
4. Additional studies are needed to confirm the above listed effect of activated charcoal, and to determine the effect of *Nigella sativa* on the immune system when given in different dosage and when used in subjects with severely suppressed immune functions.

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PHARMACOLOGICAL EVALUATION OF THE ANTI-INFLAMMATORY ACTIVITY OF CERTAIN MEDICINAL PLANTS*

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INTRODUCTION

The plants *Withania somnifera* ("Asgandh Nagori; Aaksan"), *Merendra persica* ("Suranjan Sheerin"), *Pyrethrum indicum* ("Buzidaan") and *Alpinia galanga* ("Khulanjan Kabeer") have been mentioned as useful remedies for the treatment of diverse types of ailments in various ancient, as also in recent, texts. *Withania somnifera* roots have been used, both internally and externally, in rheumatism and as resolvent, tonic, alterative, aphrodisiac and uterotonic and as a prospective substitute for *Merendera persica* corm[1, 2] which has been advocated by Al-Razi[3], Bu-Ali-Seena[4] and Ibn-al-Baytar[5] as an effective remedy for the treatment of rheumatism, gout, pain, constipation, sexual debility, muscular stiffness and rheumatic pain, and as alterative, aperient, laxative and in the diseases of liver and spleen[1], some of these actions being almost identical to that of *Pyrethrum indicum* root[1, 2, 4, 5]. Similarly, *Alpinia galanga* rhizome has been recommended for rheumatism, catarrhal affections[2], visceral pain and as digestant and carminative[3,4,5] and also as aphrodisiac[1]. Critical overview of these texts, thus, revealed that, in common, the above-mentioned plants have been persistently, and particularly, recommended, over the centuries, for the treatment of rheumatoid syndrome. Indeed, a combination of these plants has been found encouragingly effective in the treatment of clinical arthropathies in human subjects[6]. These informations, therefore, prompted us to undertake the present investigation to pharmacologically evaluate the anti-inflammatory and anti-arthritic activity of the above-mentioned plants, individually and combinely, using certain relevant experimental models inorder to vindicate the claims made by the ancient scholars and traditional healers.

MATERIALS AND METHODS

PLANT MATERIALS

Dried roots of *Withania somnifera* and *Pyrethrum indicum,* corm of *Merendra persica* and rhizome of *Alpinia galanga* were used in the present study.

EXTRACTION PROCEDURE

The plant materials were finely powdered with the help of a high speed grinding machine and the resultant powder was sieved through a sieve (pore size 0.25 mm). The powder was then extracted with Sorensen buffer (pH 7.5); to each 100 gm of powder 2.5 litre of buffer was added. The extraction was done at 37°C for 5 hours during which period the mixture was continuously stirred (at a rate of 250 stirrings per minute) with the help of

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an electrical stirrer (Laboratory Supply Conpany, West Germany). Thereafter, the supernatant was filtered through Whatman filter paper No. 1. The filtrate, thus obtained, was stored at 4°C for experimental use.

DRUGS AND CHEMICALS

Carrageenan Type V, Freund's adjuvant, Bradykinin triacetate salt, Prostaglandins E_2 and $F_2 \propto$ (Sigma, U.S.A.) Histamine dihydrochloride, 5-hydroxytryptamine creatinine sulphate (B.D.H., England), Oxyphenbutazone (Tanderil; Geigy, Switzerland), Dexamethasone (Roussel, England) and anaesthetic ether (May & Baker, England).

DOSES

Unless otherwise mentioned, dexamethasone, oxyphenbutazone and the extracts were administered, orally, in doses of 5, 100 and 500 mg/kg body weight respectively.

ANIMALS

Inbred Wistar rats weighing between 150 - 300 gm of either sex were used in the study. The animals were maintained on standard pellet diet (86/A; Bugbrooke Mills, Northampton) and *ad lib* water.

INDUCTION OF RAT PAW OEDEMA BY CARRAGEENAN

(i) Assay of the oedemagenic action of carrageenan:

Forty rats, of either sex were randomly divided into groups of 10. Initial volume (ml) of the right hind paw upto a fixed mark at the level of lateral malleolus of each rat was recorded by means of a plethysmometer (Ugo Basile, Italy). Thereafter, the rats of separate groups were respectively injected, under the plantar aponeurosis, with 0.1, 0.25, 0.5 and 1.0% carrageenan solution (0.1 ml) in normal saline and the paw volume was again recorded after 3 hours. Percentage increases in paw thickness were calculated and compared for different groups separately. Allowance was made for the non-specific effect of the saline injection by subtracting the value obtained for the contralateral saline-injected control paw from that of the test paw at the time of measurement[7]. The animals were then sacrificed at the end of 3 hr using excess of anaesthetic ether, the plantar tissue collected and processed for histological examination.

(ii) Effect of the extracts on the temporal course of carrageenan-induced inflammatory process:

Oedema was induced[8] in rats by single sub-plantar injection into the right hind paw of a solution of carrageenan (0.1 ml; 0.5%). Paw swelling was monitored as percentage change in dorso-ventral paw thickness which was measured immediately before, and at 1, 2, 3 and 4 hr after injection. The extracts or the comparable volume of distilled water were fed 1 hr before carrageenan.

(iii) Effect of the combined extract or oxyphenbutazone:

Acute oedema of the right hind paw was induced by 0.1 ml of 0.5% carrageenan injected under the plantar aponeurosis. The paw volumes were determined, 3 hr after carrageenan injection, both in the control and treated animals. The animals were pretreated with the test drugs, orally, 1 hr before carrageenan. In some experiments, the animals were pretreated for 24, 48, 72 and 96 hr at 24-hourly intervals, the last administration being 1 hr before carrageenan. Control animals received comparable volume of distilled water at similar occasions.

INDUCTION OF RAT PAW OEDEMA BY CERTAIN MEDIATORS OF INFLAMMATORY PROCESS

The oedema was produced[9] by intraplantar injection of 0.1 ml of histamine dihydrochloride (10 mg/ml), 5-hydroxytryptamine creatinine sulphate (0.05 mg/ml), bradykinin (0.05 mg/ml) and prostaglandin E_2 (0.005 mg/ml). The volume of oedema was determined ½, 1 and 2 hr after histamine or bradykinin, 1, 1½ and 2 hr after 5-hydroxytryptamine and ¼, ¾, 1½ and 2 hr after prostaglandin E_2 injection. The extracts, or comparable volume of distilled water, were fed 1 hr before injection of the phlogistic agents.

ESTIMATION OF HISTAMINE AND 5-HYDROXYTRYPTAMINE CONTENTS IN THE PLANTAR TISSUES

Rats from both the control and the extract treated groups were sacrificed 1 hr after the intraplantar injection of carrageenan, the plantar tissues collected and extracted in 10% trichloracetic acid for histamine and in acetone for 5-hydroxytryptamine by the method of Parrot and West[10]. The extracts were assayed on isolated guineapig ileum for histamine[11] and on isolated rat fundus for 5-hydroxytryptamine[12, 13].

COTTON PELLET GRANULOMA

Sterile cotton pellets 10 mg each were implanted[14] bilaterally in pectoral and groin regions of rats under ether anaesthesia. Cotton 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 the pellets.

ADJUVANT-INDUCED ARTHRITIS

Freund's adjuvant (0.1 ml) was administered by single intraplanter injection into the right hind paw[15,25]. Drugs were fed once daily starting one day prior to adjuvant injection until day 14. The oedema volume was recorded immediately before and on days 1 (4 hr after adjuvant injection), 2, 3, 5, 7, 8, 10, 12, 14 and 15. The volume of the contralateral paw was also recorded simultaneously on all occasions. The primary response was characterised by the swelling of the injected paw and the delayed systemic or secondary response was characterised by the swelling of the contralateral hind paw, the forelimb paws and the appearance of nodules on the pinna and the tail.

CALCULATION OF THE INHIBITORY EFFECT OF TEST DRUGS

The anti-inflammatory activity has been expressed[16] as per cent inhibition of the oedema volume/weight of the granulomatous tissue which was calculated by the formula - $(1 - T/C) \times 100$, where T and C are the mean values of the drug-treated and the control groups respectively.

ISOLATED TISSUES

Pieces of rat fundus[12], guineapig ileum, oestrogenized rat uterus, rabbit jejunum or frog rectus abdominis muscle[17] were suspended in 10 ml capacity isolated tissue bath containing Tyrode (37°C), Krebs (37°C), deJalon (31°C), or amphibian Ringer (room temperature - 21-22°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[18], 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 and the uterine horns were used.

GROSS BEHAVIOURAL STUDIES

The effect of the extract was studied[19] on the gross behavioural changes in rats (200-250 gm) and mice

(20-30 gm) of either sex randomly divided in groups of 10. The extract in varying doses (0.5, 1.0, 1.5 and 2.0 gm/kg) were administered *per os* and gross behavioural changes were recorded at 15, 30, 60, 120, 180 and 240 minutes.

LD_{50} STUDIES

Adult rats (150-300 gm) and mice (25-30 gm) of either sex were randomly divided in groups of 10. Graded doses of the extract (0.5, 1.0, 1.5 and 2.0 gm/kg) were fed to separate groups once and the mortality recorded for the next 8 days.

STATISTICAL ANALYSIS

The changes in the paw volume, amine concentrations or the granulomatous tissue were calculated as mean ± s.e.m. and the differences between groups evaluated statistically using Student's unpaired t - test.

RESULTS

CARRAGEENAN - INDUCED OEDEMA OF THE RAT PAW

Assay of the oedemagenic action of carrageenan:

The results are presented in Table I. The oedemagenic action of carrageenan was dose-dependent in that the degree of oedema formation was directly proportional to the concentration of carrageenan injected. Thus 0.1, 0.25, 0.5 and 1.0% concentrations of carrageenan (in 0.1 ml volume) increased the paw volume by 11.20, 26.39, 53.05 and 57.07% respectively; equal volume of normal saline increased the volume only by 0.3%. Histological examination revealed that upto a concentration of 0.5%, the degree of vascularity, exudation and oedema production was roughly related to the dose-increments; a decline was noticed with 1.0% concentration. Based on these observations, 0.5% concentration of carrageenan was used in all the experiments of the present study.

Effect of the extracts on temporal course of carrageenan-induced inflammatory process:

Table II summarizes the effect of different extracts as also of oxyphenbutazone and dexamethasone on oedemagenic action of carrageenan. In control group of animals, the mean initial paw volume was 1.44 ± .057 ml which increased to 2.03 ± .123, 2.34 ± .164, 2.57 ± .152 and 2.61 ± .155 ml (by 40.91, 62.8, 78.80 and 81.25%) at 1, 2, 3 and 4 hr respectively. At similar intervals in *Withania somnifera*-treated group, the paw volume (1.44 ± .038 ml) increased to 1.79 ± .034, 1.93 ± .074, 2.02 ± .130 and 2.07 ± .128 ml; thus it inhibited the carrageenan effect by 42.27 ($P < .05$), 46.66 ($P < .01$), 49.55 ($P < .001$) and 46.08 ($P < .01$) percent respectively. *In Merendra persica* treated group, the paw volume (1.53 ± .127 ml) increased to 1.84 ± .126, 2.01 ± .151, 2.14 ± .141 and 2.15 ± .131 ml at 1, 2, 3 and 4 hr respectively; hence, it inhibited the carrageenan effect by 49.06 ($P < .05$) 46.66 ($P < .01$), 46.01 ($P < .01$) and 46.55 ($P < .001$) percent respectively. *Alpinia galanga* failed to antagonize the oedemagenic effect of carrageenan. *Pyrethrum indicum* produced maximum inhibition (62.64%; $P < .01$) at the first hour which declined to 38.88 ($P < .05$) and 38.04 ($P < .01$) percent at the second and third hours; at the fourth hour, its inhibitory effect (22.4%) became insignificant. Combined extract from all the four plants produced comparatively better inhibitory effect wherein the initial paw volume (1.32 ± .042 ml) increased to 1.47 ± .029, 1.67 ± .048, 1.75 ± .093 and 1.82 ± .076 ml at 1, 2, 3 and 4 hr respectively; thus, it reduced the carrageenan effect by 72.23 ($P < .01$), 57.78 ($P < .001$) and 53.39 ($P < .001$) percent at the respective intervals. Dexamethasone inhibited the carrageenan response by 72.83 ($P < .001$), 80.00 ($P < .001$), 73.45 ($P > .001$) and 74.13 ($P > .001$) percent at respective

intervals. However, the effect of oxyphenbutazone was weaker, in that, it inhibited the carrageenan oedema by 32.08, 36.66, 32.74 and 27.01%, the last two figures being significant at $< .05$ level.

EFFECT OF THE COMBINED EXTRACT AND OXYPHENBUTAZONE IN RELATION TO THE INCREMENTS IN PRETREATMENT PERIODS

Results are presented in Table III. In 1 hr pretreated group, carrageenan increased the paw volume from $1.70 \pm .048$ to $2.89 \pm .076$ ml in controls, from $1.59 \pm .052$ to $2.03 \pm .061$ ml in the extract-treated and from $1.64 \pm .043$ to $2.55 \pm .058$ ml in oxyphenbutazone-treated rats; thus, the extract inhibited the oedema by 46.93 ($P < .001$) and oxyphenbutazone by 28.10 ($P < .05$) percent. On increasing the duration of pretreatment to 24 hr, the effect of the extract remained almost unchanged but that of oxyphenbutazone markedly enhanced, the percent inhibition being 34.17 ($P < .05$). However, by increasing the duration of pretreatment further to 48, 72 and 96 hr, the extract proportionately and significantly ($P > .001$) inhibited the carrageenan-induced oedema by 62.07, 75.82 and 84.78% respectively; the respective values for oxyphenbutazone were 54.64, 89.32 and 78.63%.

EFFECT OF THE EXTRACTS ON HISTAMINE-INDUCED OEDEMA

Results are summarised in Table IV. Histamine increased the paw volume from $1.61 \pm .04$ to $2.58 \pm .08$, $2.31 \pm .11$, $2.22 \pm .09$ and $2.17 \pm .09$ ml after ½, 1, 1½ and 2 hr respectively. Thus, the maximum increase was at ½ hr (60.24%) which sharply declined at 1 hr (43.47%) and thereafter gradually at 1½ (37.80%) and 2 hr (35.1%). *Withania somnifera* and *Merendra persica* had no effect on the oedemagenic effect of histamine. However, *Alpinia galanga* and *Pyrethrum indicum* effectively and significantly antagonised the histamine response; the respective percent inhibitions were 49.48 ($P > .01$), 58.57 ($P < .001$) and 34.42 ($P < .05$) for *Alpinia galanga* and 70.10, 91.42 and 98.36 for *Pyrethrum indicum* ($P > .001$). The combined extract of the four plants significantly inhibited the histamine response, at the initial stages by 43.29 ($P < .001$) and 30.00 ($P < .01$) percent at ½ and 1 hr respectively; at the later stage (1½ hr) the degree of inhibition became insignificant (16.39%).

EFFECT OF THE EXTRACTS ON 5-HYDROXYTRYPTAMINE-INDUCED OEDEMA

The results are presented in Table V. In control group of animals, 5-hydroxytryptamine increased the paw volume from $1.49 \pm .05$ ml to $2.43 \pm .11$, $2.40 \pm .11$ and $2.35 \pm .10$ ml at 1, 1½ and 2 hr respectively, the respective percent increases being 77.96, 69.34 and 68.17. *Withania somnifera* failed to significantly antagonise (13.82%) its effect at the first hour but subsequently inhibited ($P < .01$) it by 34.14 and 39.53% at 1½ and 2 hr respectively. *Merendra persica* and *Alpinia galanga* were highly effective, in that, the former suppressed ($P < .01$ to $< .001$) the oedema by 38.29, 40.24 and 65.11% and the latter by 30.85, 41.46 and 53.48% at 1, 1½ and 2 hr respectively. However, like *Withania somnifera, Pyrethrum indicum* also did not inhibit the 5-hydroxytryptamine response at the initial stage (1 hr) but susequently inhibited it by 31.70 ($P < .05$) and 60.46 ($P < .001$) percent at 1½ and 2 hr respectively. The combined extract effectively and significantly inhibited the oedema at all the three intervals by 24.46 ($P < .01$), 39.82 ($P < .001$) and 51.39 ($P < .001$) percent.

EFFECT OF THE EXTRACTS ON BRADYKININ-INDUCED OEDEMA

The results are summarised in Table VI. In control group of animals, bradykinin increased the paw volume from $1.45 \pm .04$ ml to $1.91 \pm .07$, $1.95 \pm .09$ and $1.93 \pm .09$ ml at ½, 1 and 1½ hr respectively, the respective percent increases being 31.50, 34.24 and 32.87. Whereas *Withania somnifera, Merendra persica* or

Pyrethrum indicum failed to significantly antagonise the bradykinin response at the initial stage (½ hr), that of the *Alpinia galanga* highly, persistently and significantly inhibited ($P < .001$) it by 89.13, 96.00 and 97.91% at ½, 1 and 1½ hr respectively. However, the former three plants also antagonised ($P < .01$) the bradykinin response at subsequent stages (1 and 1½ hr). The combined extract effectively and significantly ($P < .01$) inhibited the bradykinin response by 58.69, 46.00 and 52.08% at ½, 1 and 1½ hr respectively.

EFFECT OF THE EXTRACTS ON PROSTAGLANDIN E_2-INDUCED OEDEMA

The results are presented in Table VII. *Withania somnifera* markedly and significantly ($P < .001$) inhibited the prostaglandin response by 85.71, 83.33, 86.95 and 81.81% percent at 15, 45, 90 and 120 minutes respectively. Similarly, *Alpinia galanga* produced high degree ($P < .001$) of inhibition; the respective values were 82.14, 78.57, 95.65 and 81.18%. However, *Merendra persica*-induced inhibition was comparatively lesser, but significant, in that it inhibited, at the respective intervals, the prostaglandin-induced oedema by 51.65, 62.45, 60.28 and 59.43%. *Pyrethrum indicum* was entirely ineffective. The combined extract of all the four plants effectively and significantly ($P < .001$) reduced the prostaglandin effect by 57.14, 73.91, 69.56 and 86.36% at the respective intervals.

EFFECT OF THE COMBINED EXTRACT ON TISSUE HISTAMINE CONCENTRATION

The results are summarized in Table VIII. The concentration of histamine in the planter tissue of the normal paw was estimated to be 70.70 ± 2.60 ug/gm which was markedly and significantly ($P > .001$) reduced to 44.58 ± 1.13 ug/gm in the carrageenan-injected paw. However, this reduction was significantly ($P > .001$) lower in the extract-treated animals; the percent reduction being 11.47 compared to 36.94 in the non-treated animals.

EFFECT OF THE COMBINED EXTRACT ON TISSUE 5-HYDROXYTRYPTAMINE CONCENTRATION

The results are presented in Table IX. Like histamine, carrageenan also reduced markedly and significantly ($P > .001$) the 5-hydroxytryptamine concentration from 174.31 ± 0.71 to 93.0 ± 0.37 ng/gm. However, this reduction was significantly ($P > .001$) lower in the extract-treated animals, the percent reduction being 20.83 compared to 46.64 in the non-treated animals.

EFFECT OF THE COMBINED EXTRACT, OXYPHENBUTAZONE OR DEXAMETHASONE ON COTTON PELLET-INDUCED GRANULATION TISSUE FORMATION

The results are presented in Table X. In the control group of animals, the wet and constant dry weights of the granulatous tissue were 288.01 ± 8.47 and 66.73 ± 4.54 mg respectively. The respective weights were reduced significantly ($P < .001$) to 98.41 ± 5.33 (by 56.83%) and 29.28 ± 0.95 (by 56.12%) in extract-treated, to 91.78 ± 4.46 (by 59.75%) and 27.46 ± 1.48 (by 58.85%) in oxyphenbutazone-treated and to 85.65 ± 3.15 (by 62.46%) and 26.97 ± 1.62 (by 59.69%) in dexamethasone-treated ($P > .001$) groups.

EFFECT OF THE COMBINED EXTRACT, OXYPHENBUTAZONE OR DEXAMETHASONE ON FREUND'S ADJUVANT-INDUCED ARTHRITIS

The results are presented in Table XI. In control group of rats, subplanter injection of adjuvant increased the paw volume by 30.30% after 4 hr (day 1) which further increased gradually to 44.69, 52.27, 59.84 on days 2, 3 and 5 respectively. Thereafter, the raised volume started declining, reaching the second day value on day 7 (44.69%) and nearly that of the first day on day 8 (33.33%). However, from day 10 onwards the volume again increased gradually to 37.12, 40.15 and 43.12% on days 10, 12 and 14 respectively until the end of

observation period on day 15 (44.31%). The combined extract of the four plants markedly and significantly reduced the adjuvant response by 65.0% at the 4th hr and by 37.28, 43.47 and 34.17% on days 2, 3 and 5 respectively; from day 10 onwards the reduction was more marked and highly significant, the percent reduction being 48.97, 47.16, 52.63 and 56.89 on days 10, 12, 14 and 15 respectively. The effect of oxyphenbutazone was almost similar to that of the combined extract. However, the effect of dexamethasone was greater and significance higher than oxyphenbutazone or the extract, in that, dexamethasone-influenced inhibition ranged between 72.5 and 79.66% through the course of observation period except on days 3 and 5 when the reduction was 65.29 and 54.43% respectively.

The paw volume of the contralateral limb was also recorded on similar occasions. In control group of animals, the increases in the volume ranged between 18.23 to 27.34% from days 3 to 15. The combined extract as also oxyphenbutazone reduced the increase (range by 59.83 - 68.39%). Dexamethasone, however, inhibited it by 89.08 to 97.64%. The delayed systemic response of the secondary phase was also characterised by the swelling of the front paws and the appearance of nodules on the pinna and the tail. On gross assessment of the signs, control animals scored +++± grades while those of the extract, oxyphenbutazone and dexamethasone-treated groups scored +±, + and ± grades respectively.

EFFECT OF THE EXTRACT ON ISOLATED TISSUES

Guineapig ileum:- The combined extract (0.3-3.0 mg/ml) induced dose-dependent, reversible and reproducible contractions which were abolished after antropinization of the tissue. On the antropinized tissue, the *Pyrethrum indicum* extract reversibly inhibited the spasmogenic effect of histamine dihydrochloride (.02 ug/ml) by 18.75, 43.75 and 72.5% at a dose of 0.3, 0.5, 1.0 mg/ml respectively. Amlost similar degree of inhibition was produced by the combined extract at 0.6, 1 and 2 mg/ml doses. The degree of inhibition could be overcome by increasing the dose of histamine. Thus the extracts-induced antagonism was roughly dose-dependent, reversible, consistent and competitive.

Rabbit jejunum:- The extract of *Withania somnifera* (upto 1 mg/ml) did not produce any marked effect on the pendular movements nor altered the acetylcholine response. On the other hand, extracts (0.6 mg/ml) of *Merendera persica, Alpinia galanga* or *Pyrethrum indicum* inhibited the pendular movements, and relaxed the tissue, thereafter the latter two extracts enhanced the pendular movements. The combined extract (2 mg/ml) of the four plants exerted greater effect than either of the extract alone, in that it pronouncedly inhibited the pendular movements, markedly relaxed the tissue followed by the increase in the tone and movements of the tissue.

Further, all the extracts (except that of *Withania somnifera)* separately potentiated the spasmogenic effect of acetycholine (0.05 ug/ml) by 55.55 - 66.66% at a dose of 0.6 mg/ml. Interestingly, however, the combined extract of all the four plants produced much greater degree of potentiation (116.66%) than any of the extracts alone. The extracts, which augmented the acetylcholine response, delayed the inactivation of acetylcholine (.5 ug) incubated with 0.2 ml rabbit serum. These extracts had no effect on the carbachol (.1 ug/ml)-induced contractions.

Rat fundus:- The combined extract produced dose dependent, reversible and reproducible contractile effect. However, this effect was abolished on atropinization. On the atropinized tissue, the extract produced dose-dependent relaxation. Whereas *Pyrethrum indicum* (.6 mg/ml) extract did not alter the 5-HT (.03 ug/ml) response, those of *Withania somnifera, Alpinia galanga* or *Merendra persica* (.6 mg/ml) inhibited it by 21.42, 42.85 and 28.57% respectively. However, the combined extract of the four plants (2 mg/ml) inhibited the 5-HT-induced contraction by 53.24% which was greater than any of the extracts alone.

On the other hand, on tissues atropinized with usual doses of atropine (1 mg/litre), the extracts (.3 mg/ml) of *Withania somnifera, Merendra persica* and *Alpinia galanga* markedly potentiated, by about 50-80%, the spasmogenic effects of prostaglandin E_2 and F2α. However, on the highly atropinized tissues (10 mg atropine/litre), the extracts from the latter two plants inhibited the prostaglandin E_2 response by 49.83 and 61.66% respectively. The combined extract (2 mg/ml) inhibited the same by 73.40%.

Rat uterus: On the non-atropinized tissues, the extract produced pronounced contractile effect which could be repeatedly elicited without any sign of tachyphylaxis. However, on the atropinized tissues, the extracts failed to produce direct stimulant effect; rather the extracts (.1 mg/ml) of *Merendra persica* or *Alpinia galanga,* but not *Withania somnifera* or *Pyrethrum indicum,* completely inhibited the effect of prostaglandin E_2. The combined extract of the 4 plants also produced similar degree of inhibition.

Frog rectus: The combined extract did not exert any direct effect of its own. However, it (3 mg/ml) markedly potentiated the spasmogenic effect of acetylcholine (.5 ug/ml) by about 75%. The potentiation persisted even after the extract was washed out; the tissue regained the normal reponse only after repeated exposure to, and washes of, acetylcholine. Further, it prevented the hydrolysis of acetylcholine (0.5 ug) when incubated with rabbit serum (0.2 ml). However, it did not alter the carbachol (0.5 ug/ml)-induced contractions.

GROSS BEHAVIOURAL CHANGES

The mice receiving the combined extract (1-2 gm/kg) became hyperactive and mildly aggressive together with itching in the pelvic and scrotal regions; the symptoms appeared within 30 min and persisted until 3 hr. During this period, animals frequently stood on the hind limb, sat on the hind quarter and often mounted on the fellow companions. In one group of mice, the extract was administered in promethazine (5 mg/kg) pretreated animals to study whether the itching was due to the release of endogenous histamine. Interestingly, however, this group of animals became highly depressed until 4 hr observation period. Thereafter, the animals became fully active. In the rat also, the extract (1-2 gm/kg) produced hyperactivity and itching of the hind quarter and scrotal regions.

LD_{50} STUDIES

The extract did not exert any lethal effect upto a dose of 2 gm/kg in rats or mice until 8 days of observation period.

DISCUSSION

Carrageenan, a mixture of polysacchrides composed of sulfated galactose obtained from Irish sea moss *Chondrus crispus,* has been regarded as an ideal phlogistic agent because its inflammation is inhibited by non-toxic doses of all clinically-effective anti-inflammatory drugs[20]. And, over the years, carrageenan-induced paw oedema in rats has become most extensively used inflammation model for the screening of anti-inflammatory agents[21] since it was first introduced as an assay method for such agents[22]. Further, carrageenan is devoid of antigenic properties; thus, its effect depends upon the stimulation of a local inflammatory response[23]. However, different samples of carrageenan show considerable variation in their inflammatory potency; therefore, the inflammatory dose needs to be worked out for each carrageenan sample[24]. Accordingly, the potency of the carrageenan sample used in the present study was assayed; in that, graded doses of carrageenan ranging from 0.1 to 1% was tested for the oedemagenic response. It was observed that in 0.1, 0.25 and 0.5% concentrations, carrageenan induced a clear dose-dependent oedemagenic response; however, the effect of 1% did not follow the course of linearity in that its response did

not differ much from that of 0.5%. As such, in our experiments 0.5% concentration was considered as optimal and was accordingly used in the present study. Indeed, the oedemagenic response of this concentration was roughly comparable to that obtained with 1% by other workers[7,9,16,26].

The subtle kaleidoscopic cascade of integrated events which constitute the reaction of tissue to phlogistic agent over a variable time scale is obviously mediated, modulated and orchestrated by a wide variety of chemical messengers which influence and determine vascular, extracellular and cellular sequellae, the prolixity of which follow a definite time-course of underlying processes. According to the earlier study[27], after the injection of carrageenan the first response is an increase in the output of histamine and 5-hydroxytryptamine (1½ hr), this is followed by bradykinin (2 hr) and prostaglandins release begins at about the third hr, corresponding to the amine, kinin and prostaglandin phases of inflammation. Accordingly, the effect of individual extracts was studied at hourly intervals until the 4th hr to cover-up different phases of inflammatory process. Our results indicate that *Withania somnifera* and *Merendra persica* significantly inhibited the carrageenan response through the entire 4 hr observation period, *Alpinia galanga* was entirely ineffective and *Pyrethrum indicum* was effective only upto the third hr. Based on these observations, the effect of these plants was studied separately on the oedema induced by direct injections of histamine, 5-hydroxytryptamine, bradykinin or prostaglandin E_2.

On histamine-induced oedema, *Withania somnifera* had no effect, *Merendra persica* had mild and *Alpinia galanga* and *Pyrethrum indicum* had pronounced suppressive effect. Thus, the inhibition of carrageenan response at the first hour by *Withania somnifera* and *Merendra persica* does not appear to be due to the blockade of histamine (H_1) receptors. However, denial of a role of histamine, in this situation, must now be reconsidered in-view of the recent discovery[7] that H_2 receptor antagonist partially suppress carrageenan-induced oedema which has revealed a completely different view of the role of histamine in this process. Possibly, therefore, *Withania somnifera* and *Merendra persica* suppress the early phase of inflammation by blocking the H_2 receptors which get specifically activated under the influence of carrageenan. Additionally, these extracts may also inhibit the release of endogenous histamine locally at the site of carrageenan injection. Although, *Alpinia galanga* failed to significantly suppress the carrageenan-induced oedema, it markedly inhibited that produced by histamine. Classical antihistamine-mepyramine suppresses the histamine-induced oedema[28] but not that induced by carrageenan[27]. This, therefore, indicates that *Alpinia galanga* exhibits actions similar to that of H_1 receptor blocker. *Pyrethrum indicum* suppressed the carrageenan response maximally at the first hour which sharply declined at the second and third hours and reached to insignificant levels at the fourth hour; however, its inhibitory effect against histamine-induced oedema was in the increasing order with the passage of time. Possibly, this plant has dual action both on the H_1 and H_2 receptors. Precisely, therefore, the results suggest that of the four plants, two *(Withania somnifera* and *Merendra persica)* act as H_2 blockers, *Alpinia galanga* as H_1 blocker and *Pyrethrum indicum* as blocker for both the H_1 and H_2 receptors. Notably, however, whereas *Pyrethrum indicum* inhibited, *in vitro,* the spasmogenic effect of histamine on isolated guineapig ileum, *Alpinia galanga* did not; thus, presumably, *Alpinia galanga* undergoes certain metabolic changes *in vivo* and the resultant metabolites exert inhibitory effect on histamine-induced oedema. The combined extract from all the four plants exhibited a synergistic effect in that the suppression of the first hour response of carrageenan was greater than any of the plants individually. However, its effect against histamine-induced oedema, as compared to *Alpinia galanga,* was short-lived but, during that period, was more pronounced. This could be due to certain form of interaction taking place between the four plants at the latter stages of their combined effect. Indeed, the first hour suppression of carrageenan-induced oedema by the combined extract was comparable to that produced by dexamethasone and was much higher than that by oxyphenbutazone.

On the 5-hydroxytryptamine-induced oedema, whereas *Merendra persica* and *Alpinia galanga* had

pronounced suppressive effect just from the beginning of the observation period, the effect of *Withania somnifera* and *Pyrethrum indicum* discerned 30 min later. Possibly, the latter two plants undergo certain metabolic changes in the body before they exert anti-5-hydroxytryptamine effect. However, this assumption may not be necessarily unquestionable since on the isolated rat fundus, *Withania somnifera* produced direct antagonistic effect against 5-hydroxytryptamine-induced contractions. Further studies may unravel the possible mechanism. Although *Alpinia galanga* failed to significantly suppress carrageenan-induced oedema, it markedly inhibited that produced by 5-hydroxytryptamine, as it had done for that by histamine. Apparently, this plant exerts similar action against both histamine and 5-hydroxytryptamine. Moreover, *Alpinia galanga* also inhibited the spasmogenic effect of 5-hydroxytryptamine on rat fundus. Therefore, it may be inferred, at this stage, that this plant has the ability to block the 5-hydroxytryptamine receptors. The combined extract of all the four plants significantly suppressed the 5-hydroxytryptamine oedema from the beginning until the end of observation period, thus balancing the delayed phase of the onset of the effects of *Withania somnifera* and *Pyrethrum indicum*.

Alpinia galanga almost completely suppressed the bradykinin-induced oedema; the effect being discernible from the beginning until the end of observation period. However, the remaining three plants produced their effect 30 min later. Apparently, therefore, these plants undergo certain metabolic changes before they exert their action against bradykinin. The combined extract of the four plants was comparatively less effective in suppressing the bradykinin effect than *Alpinia galanga*. Possible interaction between the four plants needs to be worked out. On the other hand, *Alpinia galanga* failed to supress the carrageenan-induced inflammation whereas the other plants did. This, therefore, indicates that *Alpinia galanga* acts directly on the bradykinin receptive sites and does not affect the release of kinins.

The prostaglandin E_2-induced oedema was suppressed highly effectively by *Withania somnifera* and *Alpinia galanga* followed by *Merendra persica; Pyrethrum indicum* was entirely ineffective. Curiously, however, *Withania somnifera* failed to antagonise the prostaglandin E_2-induced contractions of the rat uterus; thus, its action on the inflammatory site is, apparently, specific. The effect of *Alpenia galanga* appears to be again complex since, on the one hand, it failed to suppress carrageenan-induced oedema, on the other hand, it effectively inhibited the prostaglandin response both in the paw and on the uterine tissue. These findings, therefore suggest that *Alpinia galanga* blocks the direct activation of prostaglandin receptive sites and does not influence the prostaglandin release process. *Merendra persica* inhibited the carrageenan-induced oedema, the prostaglandin-induced oedema and also the prostaglandin-induced contraction of the uterine tissue. Thus, this plant appears to act both by preventing the release of prostaglandins and by blocking its receptors. *Pyrethrum indicum* failed to inhibit both the oedemagenic and the spasmogenic actions of prostaglandin but suppressed the initial stages of carrageenan-induced oedema. Thus, its effect appears to be limited only to the amine and kinin phases of inflammation. The combined extract of the four plants suppressed the oedemagenic effect of prostaglandin as it did that of carrageenan and also blocked the spasmogenic effect of prostaglandin on the rat uterus. Thus, the combined extract possibly exerts its effect by preventing the release of prostaglandins and also by inhibiting its receptors.

On increasing the duration of pretreatment periods, combined extract produced better suppression of carrageenan-induced inflammation. Apparently, the combined extract undergoes slow releasable metabolic changes and the released metabolites exert their fullest effect with the passage of time. The other possibility could be that the extract exerts or modifies some components of inflammatory system or oedema formation such as the leukocytes, blood enzymes, proteins, and precursors etc. involved in activation, release and inactivation of mediators or modulators in a slow, but effective manner. Interestinly, the course of efficacy of the extract was almost comparable to that of oxyphenbutazone.

Histamine is released locally at the site of carrageenan injection[27,29]. In the present study also significant depletion of tissue histamine has been observed. The combined extract significantly prevented the carrageenan-initiated release of histamine. Furthermore, it also prevented the local release of tissue 5-hydroxytryptamine. The modest role of 5-hydroxytryptamine in early phases of acute inflammation has been recognised[15,27]. Evidently, therefore, the combined extract suppresses, atleast the early phases of carrageenan-induced acute inflammation by preventing the release of both histamine and 5-hydroxytryptamine; additionally, however, it also influences, as discussed in the preceding paragraphs, the activation of respective receptors.

In the present study, the combined extract also prevented, significantly, the formation of granulation tissue. The cotton pellet granuloma assay is, perhaps, the most widely used method for assessing the effect of drugs on different phases of inflammation. Three phases of inflammatory response to subcutaneous implantation of pellets has been described[30]. The first, short-lasting phase, of a few hours duration, is characterized by the imbibition of the pellet with fluid of low protein content. In the second phase, lasting for 2-3 days, exudation of fluid containing protein is typical. The third phase is characterized by the appearance of collagen in granuloma, preceded by mucopolysacchride synthesis, and accompanied by the greatest increase in the number of fibroblasts. Admittedly, the cotton pellet granuloma assay is relatively good test for evaluating the anti-inflammatory activity of steroids but is less satisfactory for non-steroidal compounds[31,32]. However, in our studies not much difference was observed between the animals treated with dexamethasone and those with oxyphenbutazone or combined extract. Nonetheless, certain immuno-suppressive drugs are also capable of inhibiting the granuloma formation, apparently by an intrinsic anti-inflammatory activity[33,34]. It would, therefore, be interesting to study whether this extract possesses immunosuppressive activity.

Several different types of experimental arthritis can be induced in animals. Their similarity to human disease is a matter of debate. However, not entirely unsuccessful attempts have been made to devise animal models of the various rheumatoid diseases. Adjuvant-induced arthritis in rat is probably the best and most widely used of these models employed in the screening programs for antiinflammatory drugs[15]. Indeed, in the present study, the combined extract of the four plants significantly inhibited the adjuvant-induced arthritis in rats and its effect was almost parallel to that produced by oxyphenbutazone. It has been suggested that adjuvant-induced arthritis constitutes a delayed hyper-sensitivity response to mycobacterial antigens which is evidenced by the fact that the disease can be transmitted to normal animals by sensitized lymphocytes from afflicted animals, the disease can be prevented by excision of lymph nodes draining the side of adjuvant injection and immunity in animals exposed to tolerogenic doses of adjuvant early in life[35,36,37,38]. The severity of the disorder are known to be modified by steroidal and non-steroidal antiinflammatory drugs[15]. Thus, the effect of the combined extract in this model is of more relevance to the clinical situation. However, the arthritic syndrome can be alleviated or prevented by lymphocytotoxic drugs and antilymphocyte globulin[39] and inhibited through immunosuppression by antigenic competition[40,41,42]. It would, therefore, be interesting to study whether this extract possesses immunosuppressive activity since it also inhibited in the granulation tissue formation.

Altogether, our results may help to establish a scientific basis for the use of these plants, in crude form, as an anti-inflammatory and antiarthritic remedy. The inhibition of the acute 3 hr swelling reflects the effectiveness of the combined extract on the acute inflammatory response. We also obtained evidence that the extract not only prevents oedema but is of comparable efficacy to oxyphenbutazone in inhibiting the development of granulation tissue and the adjuvant-induced arthritis. These findings might prompt the view that, pharmacologically speaking, this extract represents another example of non-steroidal anti-inflammatory agent. However, further studies are required to elucidate the activity of the extract with respect to its effect on (i) enzymes necessary for the synthesis and release of mediators, (ii) complement levels and its activation, (iii)

process of mononuclear cell exudation etc. inorder to understand the mechanism by which extract interferes with various inflammatory and immunopathological reactions. Further, anti-inflammatory as distinct from immunosuppressive activity has been described in several models of experimental inflammation for immunosuppressive agents[15] such as mercaptopurine, methotrexates, cyclophosphamide, chlorambucil and actinomycin-D. These drugs mainly act by preventing the participation of macrophages in delayed hypersensitivity and their infiltration into an inflammatory site. Similarly, a number of anti-inflammatory agents such as steroids, aspirin-like drugs, gold salts and pharmacological doses of oestrogen etc. have been shown to interfere with the immunopathological and inflammatory reactions such as adjuvant-induced arthritis. In view of these, it would be interesting to extend such studies on the extract as an immunosuppressive agent and elucidate its role in various immunopathological reactions as well as in experimental tumors in animal models.

SUMMARY

The crude aqueous extracts of the dried roots of *Withania somnifera* and *Pyrethrum indicum,* corm of *Merendra persica* and rhizome of *Alpinia galanga* were screened for their anti-inflammatory activity, either individually or combinely, against the oedemagenic action of carrageenan and certain parmacological mediators (histamine, 5-hydroxytryptamine, bradykinin and prostaglandin E_2), the cotton pellet-induced granulation tissue formation and the adjuvant-induced arthritis in rats. Excepting *Alpinia galanga,* the remaining three plants significantly inhibited the carrageenan response. However, *Alpinia galanga* effectively antagonized the response of mediators; the effect of other plants and of their combined extract against mediators was variable. The combined extract of the four plants produced highly pronounced suppressive effect against carrageenan-induced oedema and the carrageenan initiated release of histamine and 5-hydroxytryptamine. The combined extract also inhibited the cotton pellet induced granulation tissue formation and the adjuvant-induced arthritis. Its effect in these models was comparable to that of oxyphenbutazone. Possible mechanism of action has been discussed. The findings convincingly support the clinical usefulness of these plants in the treatment of rheumatoid syndrome and other inflammatory disorders.

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TABLE I: ASSAY OF THE OEDEMAGENIC ACTION OF CARRAGEENAN IN THE RAT HINDPAW (n = 10)

Group	Paw volume (ml)		% increase
	0 hr	3 hr	
Saline	1.65 ±.17	1.65 ±.17	0.30
Carrageenan 0.1%	1.71 ±.16	1.91 ±.17	11.20
0.25%	1.65 ±.18	2.09 ±.17	26.39
0.5%	1.59 ±.16	2.43 ±.16	53.05
1.0%	1.69 ±.17	2.66 ±.18	57.07

TABLE II: EFFECT OF THE EXTRACTS, DEXAMETHASONE OR OXYPHENBUTAZONE ON THE TEMPORAL COURSE OF CARRAGEENAN-INDUCED INFLAMMATORY PROCESS.

Group	Number of animals	Percent inhibition of swelling			
		HOURS			
		1	2	3	4
Control	12	—	—	—	—
Withania somnifera	9	42.27*	46.66**	49.55***	46.08**
Merendra persica	11	49.06*	46.66**	46.01**	46.55***
Alpinia galanga	10	30.39	30.00	23.89	16.37
Pyrethrum indicum	10	62.64**	38.88*	38.04**	22.4
Combined extract	11	72.23**	57.78**	58.66***	53.39***
Dexamethasone	10	72.83***	80.00***	73.45****	74.13****
Oxyphenbutazone	8	32.08	36.66	32.74*	27.01*

* $P < .05$; ** $P < .01$; *** $P < .001$; **** $P > .001$

TABLE III: INHIBITION BY THE COMBINED EXTRACT OR PHENYLBUTAZONE OF CARRAGEENAN - INDUCED INFLAMMATION. RATS WERE PRETREATED FOR VARYING PERIODS. NUMBER OF ANIMALS IN EACH GROUP ARE GIVEN IN THE PARENTHESES.

Pretreatment duration (hr)	Control Oedema %	Percent inhibition of swelling	
		Extract	Oxyphenbutazone
1	70.2 (16)	46.93*** (9)	28.10* (9)
24	68.4 (8)	47.60** (9)	34.17* (6)
48	73.5 (9)	62.07*** (9)	54.64*** (10)
72	70.4 (7)	75.82*** (9)	89.32*** (10)
96	66.0 (7)	84.78*** (10)	78.63*** (8)

Control values show percent increases in paw volume.
* P < 0.05; P** < 0.01; P*** > 0.001

TABLE IV: EFFECT OF THE EXTRACTS ON HISTAMINE - INDUCED OEDEMA OF THE RAT HIND PAW.

Groups	Number of animals	Percent inhibition of swelling		
		HOURS		
		½	1	1½
Control	16	—	—	—
Withania somnifera	15	6.18	1.42	4.91
Merendra persica	16	8.55	8.53	6.52
Alpinia galanga	16	49.48**	58.57***	34.42*
Pyrethrum indicum	14	70.10****	91.42****	98.36****
Combined extract	18	43.29***	30.00**	16.39

* P < .05; ** P > .01; *** P < .001; **** P > .001

TABLE V: EFFECT OF THE EXTRACTS ON 5-HYDROXYTRYPTAMINE-INDUCED OEDEMA OF THE RAT HIND PAW

Group	Number of animals	Percent inhibition of swelling		
		HOURS		
		1	1½	2
Control	15	—	—	—
Withania somnifera	14	13.82	34.14**	39.53**
Merendra persica	14	38.29**	40.24**	65.11***
Alpinia galanga	12	30.85**	41.46**	53.48***
Pyrethrum indicum	11	20.21	31.70*	60.46***
Combined extract	15	24.46**	39.82***	51.39***

*P < .05; ** P > .01; *** P < .001

TABLE VI: EFFECT OF THE EXTRACTS ON BRADYKININ-INDUCED OEDEMA OF THE RAT HIND PAW

Groups	Number of animals	Percent inhibition of swelling		
		HOURS		
		½ HR	1 HR	1½ HR
Control	12	—	—	—
Withania somnifera	10	2.17	48.00*	50.00*
Merendra persica	10	39.13	56.00*	66.66*
Alpinia galanga	13	89.13**	96.00**	97.91**
Pyrethrum indicum	9	26.08	52.00*	58.33*
Combined extract	12	58.69*	46.00*	52.08*

* P < .01; ** P < .001

TABLE VII: INHIBITION OF PROSTAGLANDIN E_2 - INDUCED OEDEMA BY THE EXTRACTS

Groups	Number of animals	Percent inhibition of swelling			
		MINUTES			
		15	45	90	120
Control	10	—	—	—	—
Withania somnifera	9	*85.71***	83.33**	86.95**	81.81**
Merandra persica	13	51.65*	62.45**	60.28**	59.43**
Alpinia galanga	11	82.14**	78.57	95.65*	81.81*
Pyrethrum indicum	10	10.71	7.12	4.34	4.54
Combined extract	12	57.14*	73.91**	69.56**	86.36**

* $P < .01$; ** $P < .001$

TABLE VIII: EFFECT OF THE COMBINED EXTRACT ON HISTAMINE (ug/gm) CONCENTRATION IN RAT PLANTER TISSUES LOCALLY INJECTED WITH CARRAGEENAN. TWELVE TISSUES IN EACH EXPERIMENT.

Group	Mean ± s.e.m. concentration	Percent reduction	P value
Normal paw	70.70 ±2.60	—	—
Carrageenan treated paw	44.58** ±1.13	36.94	> .001
Paw from the extract-fed and carrageenan-injected animals	62.59* ±0.83	11.47	

* $P < .001$; ** $P > .001$.

TABLE IX: EFFECT OF THE COMBINED EXTRACT ON 5-HYDROXYTRYPTAMINE (ng/gm) CONCENTRATION IN RAT PLANTER TISSUES LOCALLY INJECTED WITH CARRAGEENAN. TWELVE TISSUES IN EACH GROUP.

Group	Mean ± s.e.m. concentration	Percent reduction	P value
Normal paw	174.31 ±0.71	—	
Carrageenan-treated paw	93.00* ±0.37	46.64	> .001
Paw from the extract-fed and carrageenan-injected animals	137.06* ±1.60	20.83	

* P > .001

TABLE X: EFFECT OF THE COMBINED EXTRACT, OXYPHENBUTAZONE OR DEXAMETHASONE ON COTTON PELLET - INDUCED GRANULATION TISSUE FORMATION.

Group	Number of animals	Mean ± s.e.m. weight (mg)		Percent reduction	
		Wet	Dry	Wet	Dry
Control	14	288.01 ±8.47	66.73 ±4.54	—	—
Combined extract	15	98.41 ±5.33	29.28 ±0.95	56.83*	56.12*
Oxyphenbutazone	10	91.78 ±4.46	27.46 ±1.48	59.75*	58.85*
Dexamethasone	12	85.65 ±3.15	26.97 ±1.62	62.46**	59.69**

* P < .001; ** P > .001

TABLE XI: EFFECT OF THE COMBINED EXTRACT, OXYPHENBUTAZONE OR DEXAMETHASONE ON ADJUVANT-INDUCED ARTHRITIS (n=10)

Group	DAYS										
	Mean ± s.e.m. volume of right hind paw (% inhibition Vs. control)										
	0	1	2	3	5	7	8	10	12	14	15
Control	1.32 ± .03	1.72 ± .03	1.91 ± .04	2.01 ± .04	2.11 ± .03	1.91 ± .03	1.76 ± .03	1.81 ± .04	1.85 ± .05	1.89 ± .07	1.90 ± .05
Combined extract	1.34 ± .03	1.48 ± .04 (65.00) ****	1.71 ± .03 (37.28) **	1.73 ± .04 (43.47) ***	1.86 ± .03 (34.17) ***	1.73 ± .04 (33.89) ***	1.62 ± .05 (36.36) *	1.59 ±.04 (48.97) *	1.62 ±.04 (47.16) ***	1.61 ± .04 (52.63) ***	1.59 ± .04 (56.89) ***
Oxyphenbutazone	1.32 ± .03	1.47 ± .03 (62.5) ****	1.70 ± .03 (35.59) **	1.68 ± .04 (47.82) ***	1.87 ± .04 (30.37) ***	1.72 ± .04 (32.20) **	1.63 ± .03 (29.54) *	1.56 ± .04 (51.02) ***	1.60 ± .04 (47.16) ***	1.62 ± .03 (47.36) ***	1.58 ± .04 (55.17) ***
Dexamethasone ****	1.38 ± .04	1.49 ± .02 (72.5)	1.50 ± .03 (79.66)	1.62 ± .05 (65.29)	1.74 ± .04 (54.43)	1.51 ± .03 (77.96)	1.48 ± .05 (77.27)	1.51 ± .04 (77.46)	1.51 ± .03 (75.47)	1.51 ± .03 (77.19)	1.51 ± .02 (77.58)

* $P < .05$; ** $P < .01$; *** $P < .001$; **** $P > .001$

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PRELIMINARY CLINICAL EVALUATION OF CERTAIN HERBAL REMEDIES IN THE TREATMENT OF VITILIGO*

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INTRODUCTION

Vitiligo (Bars) has been a well known disease to our Islamic Medical figures. Al-Tabari (810-895 AD)[1] has described the aetiology of the disease. Al-Rhazi (850-925 AD)[2] has given a comprehensive description of Bars, Ib-Sina (980-1037 AD)[3] has mentioned, in his famous book, Al-Qanoon, the role of tissue metabolism in Bars and mentioned that the disease can be transmitted from parent to off-spring.

Today, vitiligo is considered a common skin disorder characterized by gradual development of depigmented white patches of varying size and shapes anywhere on the skin and mucous membrane. It affects about 1% of the population and both sexes are equally affected[4]. Its onset could be at any age, but usually it is in the first decade[5]. The distribution of the lesions are multiple, bilateral and symmetrical in most of the cases. When they occur on the exposed part of the body i.e. face and back of the hands, they often lead to considerable cosmatic, social and psychological difficulties. As a result, the patients are generally disturbed mentally and may develop inferiority complex.

The exact cause of vitiligo is still unknown despite of centuries of speculation. Three major theories have been proposed to explain the pathogenesis of this obscure disease[6]—the autodestruction theory, the auto-immune theory and the neural theory.

The histopathology of vitiligo is also not quite clear and the only change is the disappearance of melanocytes in the depigmented area[7].

There is no specific treatment for vitiligo. The most widely used are photo-chemotherapy (PUVA)[8] and corticosteroids[9]. Both of these treatments are unsatisfactory and not free from serious side effects[10].

From the review of literature, it becomes evident that vitiligo in all its aspects; pathogenesis, pathology, clinical picture and therapy presents a considerable problem in medicine. All these facts stimulated our interest to study this disease with a hope to find a new approach in the treatment of this recalcitrant disease. The aim of study was to evaluate the therapeutic efficacy and safety of certain herbal remedies in the treatment of vitiligo (Bars).

MATERIAL AND METHODS

184 patients with vitiligo were selected from the outpatient clinic of Islamic Centre for Medical Sciences, Kuwait. Their age renged between 12-60 years, 94 of them were females and 90 males. They were subjected to thorough clinical examinations and laboratory investigations, including stool and urine analysis,

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complete blood count, sedimentation rate, fasting blood sugar, renal function test, liver function test, lipid profile and serum electrolytes. These investigations were done for every patient on their entry to the clinical trial and after every three months. The criterion for selection was to include such cases of vitiligo which were free from other systemic diseases. The base line data were recorded on a case sheet prepared for the purpose of the study and the depigmented areas of the body were marked out on a human sketch.

Photographs and coloured slides were taken for most of the cases before and after the treatment.

The patients were divided into three treatment groups. The first group was given oral medicine (PS) and topical application paste (Z1). The second group was given the same oral medicne (PS) and paste (Z2) for topical application and the third group was given the same oral medicine (PS) and paste (Z3) for topical application (Table 1). The patients were exposed to sun light for 5-10 minutes depending upon their tolerance.

TABLE 1: DISTRIBUTION OF THE PATIENTS ACCORDING TO THE TREATMENT GROUP

Groups	Number of patients	Male	Female	Treatment
1st	24	12	12	PS + Z1
2nd	65	30	35	PS + Z2
3rd	95	48	47	PS + Z3
TOTAL	**184**	**90**	**94**	

- The dosage of PS capsules orally given to all the patients, was two capsules in the morning and two capsules in the evening after meals, with the total dose of 3 gm.
- The application of the pastes: Z1, Z2, Z3, was done by mixing a small amount of powdered drug with water and applied on all the existing white patches. The time of retaining the paste on the patches varied from 30-60 minutes. Afterwards the paste was washed off.

The patients were put also on a special diet according to the traditional system of medicine [11], some food articles were restricted and some recommended.

Clinical follow-up was done monthly and the response to the treatment was evaluated every 3 months.

Criteria for assessment of response

Response to the treatment was assesed on the following lines:

1 - No response: no pigmentation and appearance of new lesions.

2 - Response:
1. good response (41-100% repigmentation).
2. fair response (up to 40% repigmentation).
3. poor response (no repigmentation but no new lesion developed and no increase in the size of the existing patches observed).

RESULTS

The preliminary results of the work are presented under the following headings:

I) General Observations

II) Therapeutic Response

I) General Observations

Of the 184 cases, who were selected in this study, the females were 94, while the males were 90; so the ratio of female to male was 1:1.04. The age of the patients ranged between 12 to 60 years. The duration of the disease varied from 1 month to 28 years. The number of localized type of the disease was 150 cases while the generalized type was 34 cases (Table 2).

TABLE 2: DISTRUBUTION OF THE PATIENTS ACCORDING TO THE TREATMENT GROUP

Group	1st Group	2nd Group	3rd Group	Total
Patients	24	65	95	184
Male	12	30	48	90
Female	12	35	47	94
Age	12 – 47Y	12 – 56Y	12 – 60Y	12 – 60Y
Duration	2M – 12Y	1M – 20Y	1M – 28Y	1 – 28Y
Types:				
– Localized	19	50	81	150
– Generalized	5	15	14	34

II) Therapeutic Response

Group No. 1 = PS Capsule + Z1 paste.

In this group, the drugs were tried on 24 cases. The distribution of patients according to sex, age group, duration of the disease and the clinical pieture is shown in Table 2.

The therapeutic response is detailed as follows:

i) General therapeutic response.
ii) Response in relation to sex group.
iii) Response in relation to clinical type.
iv) The side effects of the treatment.

i) GENERAL THERAPEUTIC RESPONSE:

Out of 24 cases of the group, 22 cases (92%) responded to the treatment while 2 cases (8%) did not respond.

In the responding cases, 7 cases (29%) showed poor response, 7 cases (29%) showed fair response, while 8 cases (34%) showed good response. Table 3 shows the general response in Group I treatment.

TABLE 3: GENERAL THERAPEUTIC RESPONSE TO TREATMENT

Response	Nil	Poor	Fair	Good	Total
No. of patients	2	7	7	8	24
Percentage	8%	29%	29%	34%	100%

ii) RESPONSE IN REALTION TO THE SEX GROUP:

The fair and good response was more in females' group than in Males' group. Table 4 shows the response in relation to sex group.

TABLE 4: RESPONSE IN RELATION TO SEX GROUP

Response	Nil	Poor	Fair	Good	Total
– Male	2	5	3	2	12
– Female		2	4	6	12
Total	**2**	**7**	**7**	**8**	**24**

iii) RESPONSE IN RELATION TO THE CLINICAL TYPES:

It was observed that all the cases with good response had localized vitiligo. The fair response was observed in 6 localized type and in one generalized type. Poor response was found in 4 cases with generalized types and 3 cases with localized types. No response was found in 2 localized type (Table 5).

TABLE 5: RESPONSE IN RELATION TO THE CLINICAL TYPE

Response	Nil	Poor	Fair	Good	Total
– Localized	2	3	6	8	19
– Generalized	–	4	1	–	5
Total	**2**	**7**	**7**	**8**	**24**

iv) SIDE EFFECT OF THE TREATMENT:

In Group 1-trial, no side effect was observed during the treatment.

Fig. 1,2,3,4 Show, the response in the Ist group. PS + Z1

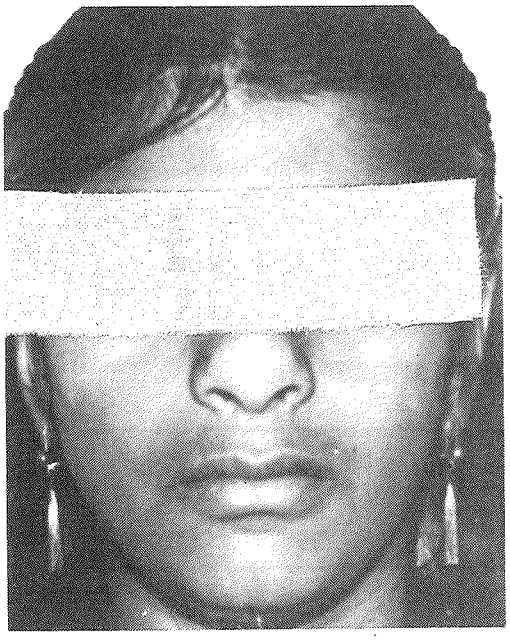

Fig.1 Before treatment

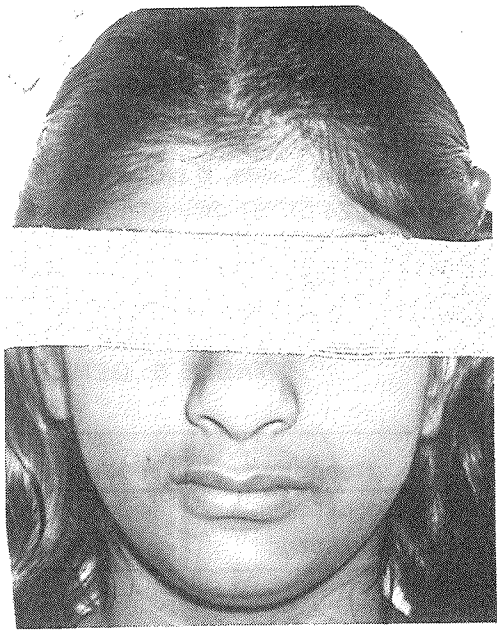

Fig.2 After treatment

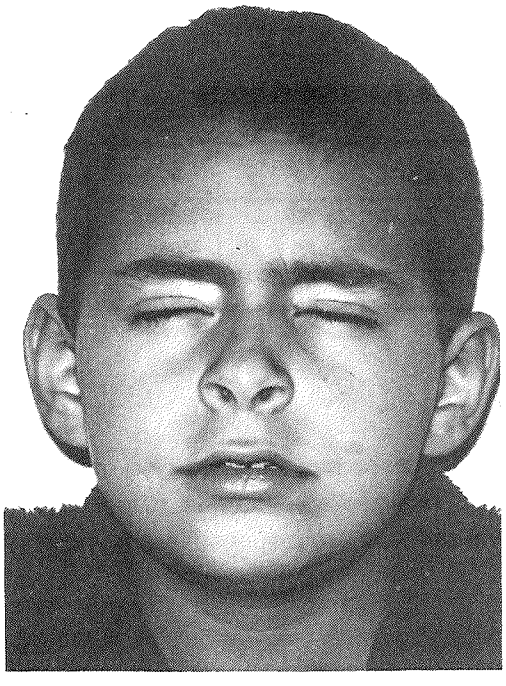

Fig.3 Before treatment.

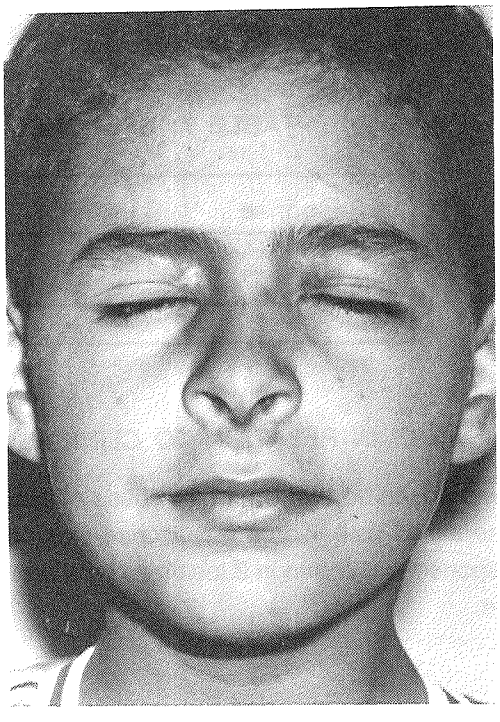

Fig.4 After treatment.

Group No. 2 = PS Capsule + Z2 paste.

The drugs were tried in this group on 65 cases. The distribution of patients according to sex, age group, duration of disease and the clinical presentation is shown in Table 2.

i) GENERAL THERAPEUTIC RESPONSE:

Out of 65 cases of the 2nd group, 64 (98.5%) responded to the treatment while 1 case (1.5%) did not respond.

In the responding cases, 8 cases (12.5%) showed poor response. Fair response was present in 32 cases (49%) while 24 (37%) showed good response; so pigmentation appeared in (86%) cases.

Complete cure 100% occured in 4 patients. Table 6 shows the general therapeutic response.

TABLE 6: GENERAL THERAPEUTIC RESPONSE

Response	Nil	Poor	Fair	Good	Total
No. of patients	1	8	32	24	65
Percentage	1.5%	12.5%	49%	37%	100%

ii) RESPONSE IN RELATION TO THE SEX GROUP:

The fair and good response was slightly more in males than in females. Table 6 shows the response in relation to sex group.

TABLE 7: RESPONSE IN RELATION TO SEX GROUP

Response	Nil	Poor	Fair	Good	Total
Male	–	1	17	12	30
Female	1	7	15	12	35
Total	**1**	**8**	**32**	**24**	**65**

iii) RESPONSE IN RELATION TO CLINICAL TYPES:

It was observed that out of 24 cases of good response, 23 cases had localized type of Vitiligo while 1 had generalized type. The fair response was observed in 22 localized types and in 10 generalized types. Poor response was found in 3 localized type and in 5 generalized type. No response was found in one localized type.

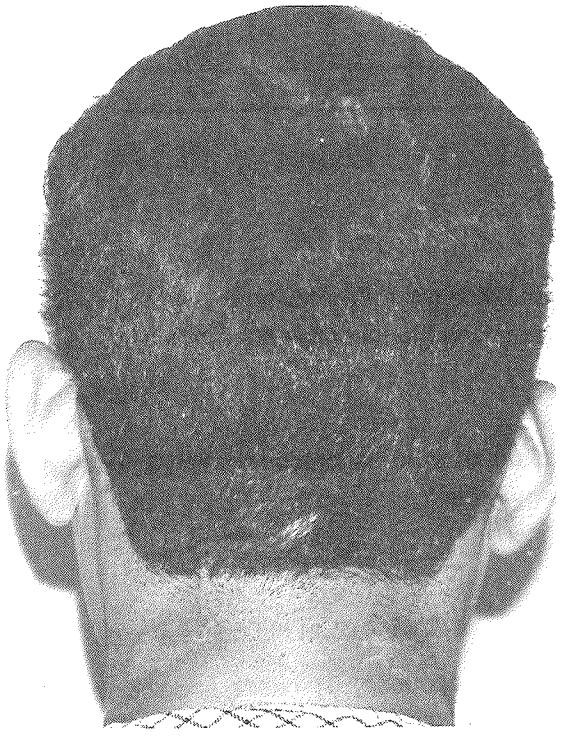

Fig.5 Before the treatment.

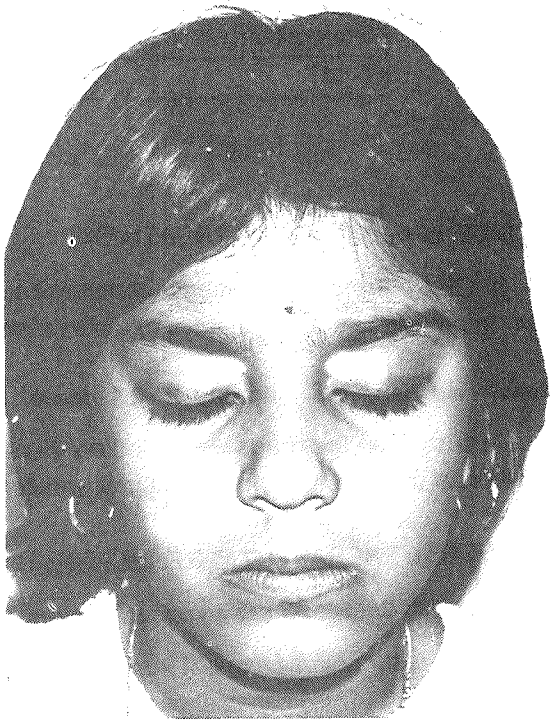

Fig.7 Before the treatment.

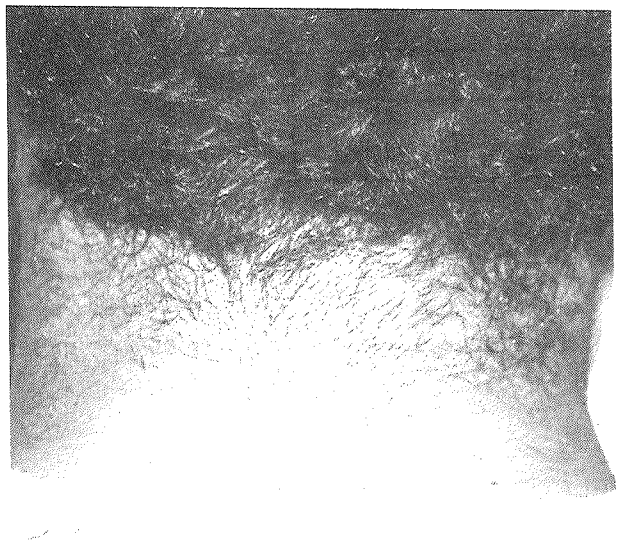

Fig.6 After the treatment.

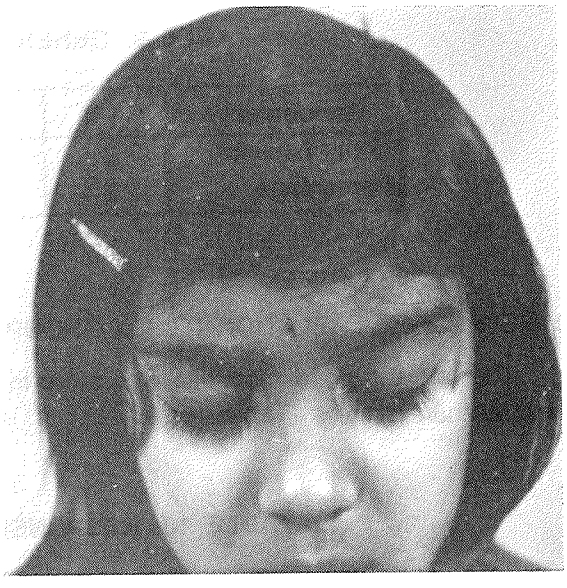

Fig. 8 After the treatment.

TABLE 8: RESPONSE IN RELATION TO CLINICAL TYPE

Response	Nil	Poor	Fair	Good	Total
Localized	1	3	22	23	49
Generalized	–	5	10	1	16
Total	**1**	**8**	**32**	**24**	**65**

iv) SIDE EFFECT OF THE TREATMENT:

In Group-II trial, few patients complained of epigastric discomfort after taking the oral medicine, which was improved after several days of the treatment and after taking the medicine after meals.

Group No. 3 = PS Capsule + Z3 paste.

In this group the drugs were tried on 95 cases. The distribution of patients according to sex, age group, duration of disease and the clinical presentation is shown in Table 2.

i) GENERAL THERAPEUTIC RESPONSE:

Out of 95 cases, 93 (98%) cases responded to the treatment while 2 (2%) did not respond.

In the responding cases, 17 cases (18%) showed poor response, 31 cases showed fair response (33%), while 45 (47%) cases showed good response. So pigmentation occured in 76 cases (80%).

Complete cure (100%) was observed in 3 cases (Table 7).

TABLE 9: GENERAL THERAPEUTIC RESPONSE

Response	Nil	Poor	Fair	Good	Total
No. of patients	2	17	31	45	95
Percentage	2%	18%	33%	47%	100%

i) RESPONSE IN RELATION TO SEX GROUP:

The fair and good response was more in males than in females, while poor response was more in females than in males (Table 10).

TABLE 10: RESPONSE IN RELATION TO SEX GROUP

Response	Nil	Poor	Fair	Good	Total
Male	1	7	19	24	51
Female	1	10	12	21	44
Total	**2**	**17**	**31**	**45**	**95**

iii) RESPONSE IN RELATION TO THE CLINICAL TYPE:

It was observed (Table 11) that, 38 cases of good response had localized vitiligo and 7 cases had generalized type.

In fair responded cases 29 had localized type while 2 cases had generalized type. In poor responded cases 12 had localized type while 5 had generalized type.

One localized type and one generalized type did not respond to treatment.

TABLE 11: RESPONSE IN RELATION TO CLINICAL TYPES

Response	Nil	Poor	Fair	Good	Total
Localized	1	12	29	38	80
Generalized	1	5	2	7	15
Total	**2**	**17**	**31**	**45**	**95**

iv) SIDE EFFECTS OF THE TREATMENT:

No singificant side effects were observed in this group. Some cases developed contact irritation from the topical application which was usually improved after discontinuing the medicine for few days, and increasing the dilutions of the paste. Some patients complained of epigastric discomfort after taking the oral medicine. These symptoms decreased with time and by taking the medicine after meals.

The general therapeutic response in the total of 184 patients

Out of 184 cases, 5 cases (3%) did not respond to the treatment while 179 cases (97%) responded to the treatment.

In the responding cases, 32 cases (17%) showed poor response; 70 cases (38%) showed fair response, while 77 cases (42%) showed good response. The results are shown in Table 12.

Complete cure was achieved in 7 cases (4%) and pigmentation occured in 147 cases (80%).

TABLE 12: THE GENERAL THERAPEUTIC RESPONSE IN ALL THE CASES STUDIED

Response	Nil	Poor	Fair	Good	Total
Group I	2	7	7	8	24
Group II	1	8	32	24	65
Group III	2	17	31	45	95
Total	**5**	**32**	**70**	**77**	**184**
Percentage	**3%**	**17%**	**38%**	**42%**	**100%**

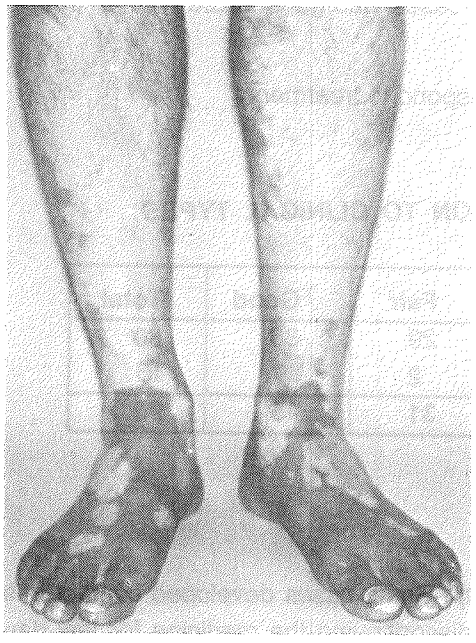

Fig.9 Before treatment.

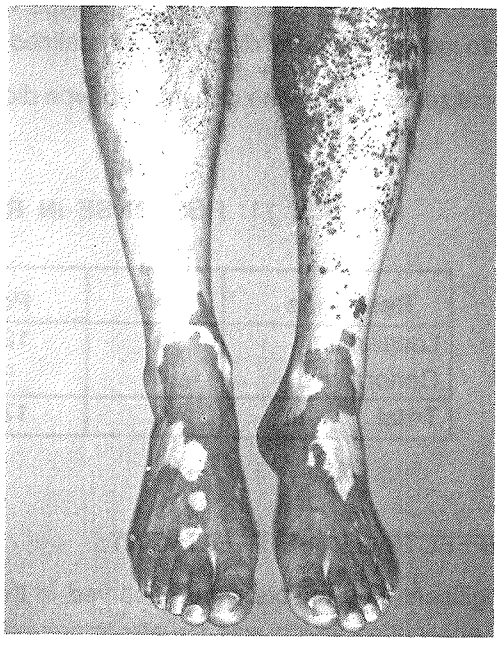

Fig.10 After treatment.

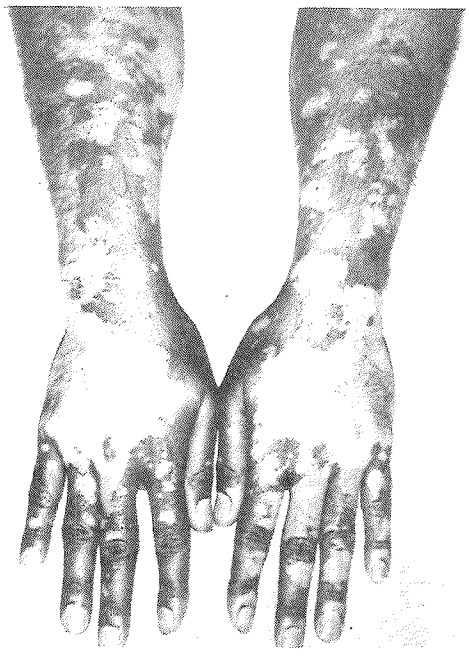

Fig.11 The same patient before treatment

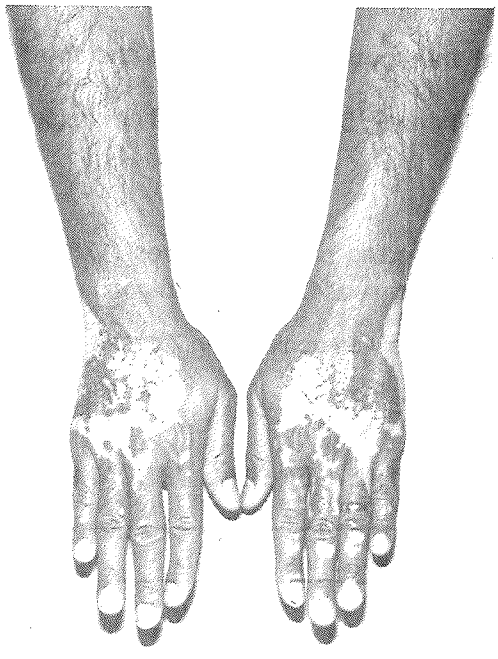

Fig.12 After treatment.

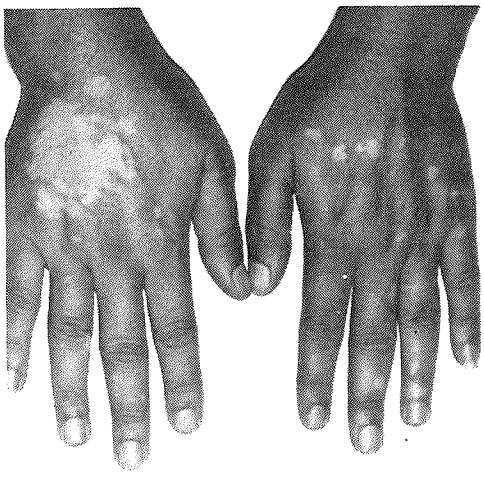

Fig.13 Before treatment.

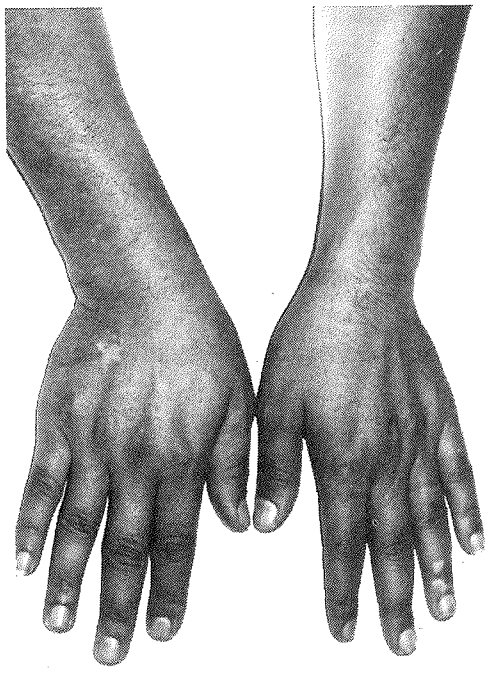

Fig.14 After treatment.

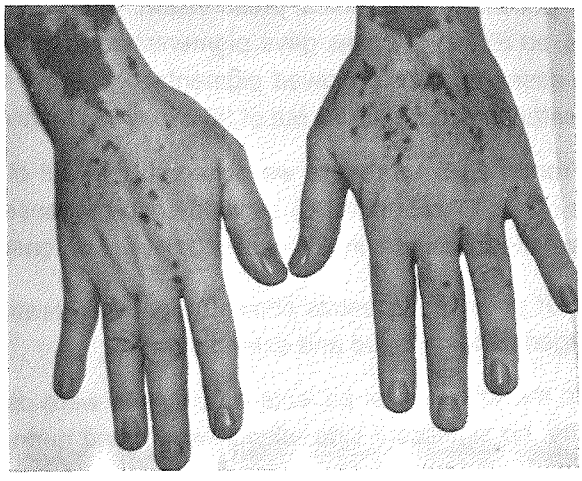

Fig.15 Before treatment.

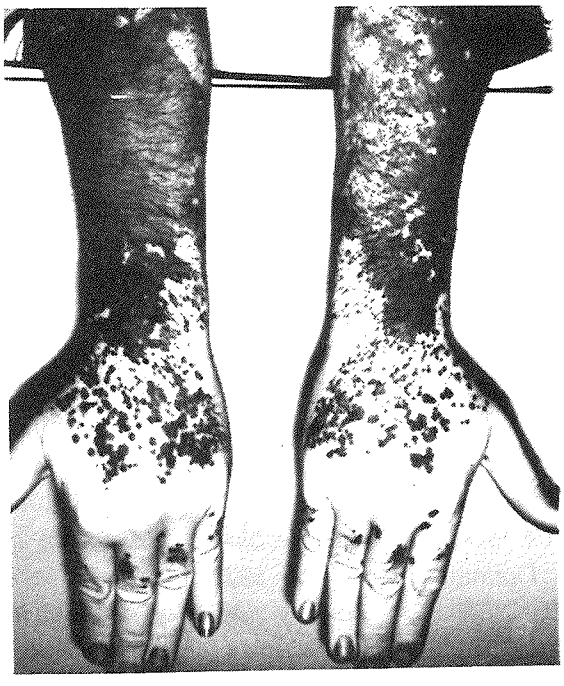

Fig.16 After treatment.

COMMENT AND CONCLUSION

Vitiligo (Bars) is well known to the medical world from time immemorial and has ever been a challenge to the medical profession. It was one of miracles associated with Jessus Christ to cure the patient of Bars by the touch of his hand. From that time till now the cure of patient with vitiligo has always been the task of all investigators who worked on this disease. Many attempts had been made for the treatment of vitiligo by Herbal remedies used by Islamic medical workers[12-16], their results were encouraging

In our study, the preliminary results of using certain remedies in the treatment of vitiligo showed that all drugs used were effective in the treatment of both localized and generalized vitiligo, irrespective of age, sex of the patients or the clinical presentation. In group I, pigmentation started to appear in 15 cases out of 24 cases, so (63%) of cases gave pigmentation response, while 29% showed poor response. In group II, out of 65 cases 56 cases showed pigmentation (86%) and 3 cases showed complete cure (5%). In group III, pigmentation occured in 79 out of 95 cases (83%) and complete cure was seen in 4 cases.

From the above results we observed that out of 184 cases, complete cure (100%) was achieved in 7 cases (4%), 77 cases (42%) showed good response and 70 cases showed fair response (38%). While no pigmentation occured in 37 cases (20%), 147 cases (80%) showed pigmentation.

Our preliminary results showed that in all treatment groups, the general response was good and encouraged us to continue and extend our trial.

In the follow up of patients no changes were observed in the investigations which were done every 3 months, no significant side effects were found during the treatment apart from few cases developing local irritation for the topical applications especially Z3 paste which was improved after the dilution of the paste.

From the above mentioned results, our study showed that the herbal remedies used in this study were effective in the treatment of vitiligo (Bars) and were safe and no side effect was noticed.

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THE ACADEMIC AND SCIENTIFIC NATURE AND VALUE OF ISLAMIC MEDICINE (TIBB-I-ISLAMI)

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PAKISTAN

The era of which Islamic medicine is the product, is no doubt ancient, but it was nevertheless an era of maturity of intellect, discretion and understanding. Man in that era had attained such heights of intellect and thought as to fully and perfectly conceive and grasp the universal truths. It was in this era that the Greek philosophers came to acquire universal recognition of their philosophical theories and logical inferences. Aristotle, Galen, Socrates and Hippocrates, all received in this period acknowledgement of their philosophical views, more than ever before. It was the very era that witnessed the auspicious birth of the great prophet of Islam (ﷺ). The process of the progress of man after passing through various phases had reached such heights as to be able to absorb and reflect effectively the lights of Islam. It is for this reason that every branch of life in that era is characterised by an upsurge of high principles, lofty ideals and the emergence of a galaxy of personalities of eminence and accomplishment. More importantly, learning in that era was learing in the true sense, its aim being the search for truth and discovery of the secrets of nature. Learning had not been polluted by any motivation for acquisition of commercial or monetary gains. The advent of Islam led to added impetus to the human mind and enabled it to shape a new world so as to continue and accelerate the process of progress. A few centuries after the advent of Islam, in addition to non-Muslims, a great number of eminent philosophers and thinkers brought up in the tradition of Islam appeared who demarcated new paths of thought and action and presented theoretical and practical plans for transforming human life. I hope you would not attribute it to exaggeration when I say that what distinguishes the old from the modern world are the same intellectual and theoretical concepts of the Islamic period which later gave birth to scientific experimentations and industrial achievements which are, in fact, the line of demarcation between the old and the modern world. Had the Islamic era not given birth to the great thinkers and philosophers and had Muslims not laid the foundation of experimentation and observation, who can say the modern world would have taken its present shape and the West would be parading with pride its industrial achievements and scientific inventions. The pages of history do support the fact that Muslims not only made contributions to ideas and thoughts but also imparted training in experimentation and observation. These contributions and training, after passing through some further stages of progress, formed the basis of the Renaissance and the industrial growth of the West. What is under consideration here is not the level of achievement in the field of industry and technology in that era but the people who were the initiators, guides and pioneers in the field of learning, research, theoretical and conceptual developments and scientific experimentations and observations. History provides an irrefutable evidence of the fact that those who occupied the place of guides and leaders in this field were persons whose minds had been trained under the light of Islam. You may call them the beginners, but remember these beginners are also the pioneers and forerunners who showed the later generations the path of progress. By no rule of morality can they be denied the place of honour and esteem they deserve. The westernized minds may admire the West, but history proclaims the fact that verification of the universal truths of philosophy by the inductive process is one of the great achievements of the Muslim philosophers. This important fact of history is highlighted by the poet of the East, Allama Iqbal in the following words:

دانه آن صحرا نشینان کاشتند
حاصلش افرنکیان بردا شتند

(The seed was sown by the desert dwellers but the produce was lifted or taken away by men of the West)

The fact to which I wish to draw your attention is that the Greek mind, despite all its greatness, could not travel beyond its logical inferences. When the Muslims took over Greek Medicine, they found it rich with logical inferences but devoid totally of experimentation and observation. The Muslim physicians soon realized this shortcoming in Greek Medicine and started to test the philosophical theories and logical inferences by putting them to experimentation also. They, thus, laid the foundation of a new medical science which on the one side was supported by logical inferences and absolute principles of philosophy and on the other the philosophical absolutes and hypotheses underwent scrutiny and verification by the inductive process. It is this new science of medicine introduced by the Muslims which we call Tibb-i-Islami and the nature and value of which is now the subject matter of our present discussion.

When science made further strides and entered the age of microscopic and chemical analysis, this traditional system of medicine was called empirical, although it was not empirical but was in the true sense a rational system. There was no aspect of this system which was not founded on science, reason and experimentation and where "whys" and "whats" had not been or could not be effectively answered by cogent reasoning. Before, however, I take up the subject of "empirical", it would be appropriate if we keep the definition of that term before us so that we may consider whether it would be proper to call this traditional system of medicine "empirical". Empirical has been defined in Webster's Dictionary in the following words:

"Relying or based solely on experiment and observation"

Similarly, the Medical Dictionary by Dr. W.A. Newman Dorland defines the term empirical as "based on experience". These definitions show that by empirical it is meant that system of treatment which is based only on experiment and which does not have at its back any logic, reasoning or philosophy, nor is it regulated by any comprehensive principle or rule of universal applicability. This is the definition of empirical which really applies to quackery or non-scientific system of treatment. The Islamic medicine which is, in true sense, a scientific system of treatment and at the back of which, at every step from the beginning to the end, are logical inferences and verifiable truths and hypotheses, was given this appellation by the Western commercial pharmaceutical concerns out of sheer prejudice. Those who are aware of Western attitude know the fact only too well that Western attitude is not only mercantile but also artful towards the Asians generally and the Muslims particularly. In order to propagate the Western medicine or in other words to develop the trade of Western medicine, it was felt necessary to condemn and injure the otherwise useful, popular and harmless system of treatment of the East.It was for this commercial imperative that Islamic Medicine was accused of being empirical and as such deserving of condemnation. What is more regrettable is that our own medical practitioners who begin their professional career after acquiring modern science of medicine and assume the title of modern doctors, betray deep influence of the West and have, in the words of Lord Macaulay, a deep imprint of the Western mind. The result is that these modern doctors of our country, too, lend support to the commercial pharmaceutical concerns of the West and ignore and disdain to examine, try and understand the herbal drugs of Islamic medicine. This has led to two-fold dangerous consequences. The first being that the valuable asset of traditional medicine which our forerunners had collected after efforts of centuries, could not advance any further. That is, no addition could be made to the herbal drugs. The other serious consequence was that this art gradually went out of the orbit of men of science and became monopolised by a class of persons who were conversant neither with modern nor classical medicine. It is this class which holds sway in

this field so far. This is thus the period of stagnation and backwardness of Islamic medicine, the signs of the end of which are now appearing in some Eastern and Western countries, and it may be expected that by the end of this century some traces of its revival will perhaps become visible. Besides the compound drugs, the collection of herbal drugs which the Muslim physicians had left by the middle of the seventeeth century, numbers more or less four hundred. This is rather a small number, but my object is not to present the data of such drugs but to explain that the nature of these drugs of Islamic medicine, irrespective of what they are and what their number be, is scientific and not empirical. The drugs are truly scientific and stand fully the test of modern science. They can be called empirical only if in the determination of their potency, characteristics or their indicated use, no reliance had been placed on any science, logic or philosophy, but on mere experience and use. It is true that microscope had not yet been invented in that age, but rational sciences did exist and the capabilities of intellectual insight and understanding were at a high stage of development. Personalities were on the scene like Ibne Haitham, the father of Optics, who in his book (كتاب المناظر والمرايا) had made detailed study of reflection and refraction of light and thus paved the way for the invention of microscope, telescope and other optical instruments. So was present (جابر بن حيان) called by the Western historians 'the father of chemistry' who by inventing various kinds of acids, gases and chemical instruments had laid the foundation of modern chemistry and science. It can be easily understood that the era which had produced towering personalities of universal and everlasting fame such as :

ابن الهيثم ـ جابر بن حيان ـ حنين ابن اسحاق ـ ثابت بن قرة ـ علي بن ربن الطبري ـ أبو بكر محمد زكريا الرازي ـ ابن البيطار ـ البيروني ـ الكندي ـ أبو القاسم الزهراوي ـ الخيام ـ ابن رشد وابن سينا .

cannot be dubbed simply as an era of quackery and empiricism. It can also be easily understood that those who had occupied the place of inventors, discoverers and pioneers in the world of learning and science, could not tolerate in their time an unscientific and unstudied system of treatment. It is a misfortune resulting mainly from undue influence of the West that the people generally tend to identify discovery, investigation and research the result only of microscopic and chemical analysis, although microscope only helps observation while chemicals act on matter. The field of potency (قواي) and characteristics (كيفيات) is outside the scope of microscopic and chemical analysis. This is the reason why while laboratory tests deal with the constituent ingredients (أجزاء تركيبي) of matter, they are silent as regards potency and characteristics, though in medical science the knowledge of the potency and characteristics of drugs is more necessary than that of their constituent ingredients. It was for this reason that the early physicians made use of rational sciences also and devised logical rules for ascertaining the potency and characteristics of drugs. For example, (علي بن سهل ربن الطبري) the first author physician of the ninth century, which is the early period, sets apart a whole chapter in his famous book (فردوس الحكمة) for ascertainment of potency of drugs and lays down logical rules for the purpose. He writes:

هذا الباب في الدلائل على قوى الأشياء من قبل ألوانها وطعومها وسائر أعراضها .

(This chapter deals with rules with the help of which the potency of things can be ascertained from their colour, taste and other characteristics). He ascertained the potency of drugs by the rules so devised by him and then proceeded to test the properties of each drug by practical experiment. At one point he, therefore, writes:

ولكل شيء قوة لا يُعرف علتها ولا يدرك غورها إلا بالتجارب

(A potency is hidden in every thing which cannot be ascertained without experiment). By these examples, I want to explain that even a physician of the early period, like(علي بن سهل ربن الطبري) considered it necessary to put every thing through the process of experiment and only after he got confirmation of his logical inferences from the experiment he laid down a rule concerning the drug. *This is the same inductive method of investigation of modern science which the Islamic physicians had adopted in the very early period and which is even now the hallmark of Western scientific system of research.* In fact it will not be out of place to say that science itself is the very name of induction which had been introduced by none other than Muslim physicians.

Here I would seek your permission to present the definition of science from which you may assess how near was the system of research in Islamic medicine to the modern methods of research, even in the absence of microscope and chemical analysis. Science is defined in the following words:

> "A branch of study which is concerned with observation and classification of facts, especially with establishment (and, strictly, the quantitative formulation) of verifiable general laws, chiefly by induction and hypothesis".

This definition of science brings out the fact that induction and hypothesis are the methods of science for acquiring the knowledge of reality. The question arises as to where from to obtain and formulate the hypothesis for starting the scientific process. This is the first stage of scientific method of research where the need to seek help from rational sciences (logic and philosophy) is felt. That is to say that the hypothesis is prepared with the help of logic and philosophy. Logic prevents the mind from falling into error in deriving inferences. In other words, the premises are so prepared that the mind is saved from error in deliberation. Thus take shape the universal principles (موجبة كلية) or (سالبة كلية) which are entirely the product of rational sciences and which we in the language of science call "hypothesis". In other words, science is dependent on the philosophical principles for its experimentations. That is why philosophy is called the mother of all sciences. Thus when a universal principle or hypothesis is ready, its verification is done by the method of induction and if a positive result ensues, the same is called a formula in the terminology of science.

I have just explained the scientific system of research. This very system of research is also practised in Tibb-i-Islami. *In Tibb-i-Islami, too, hypothesis is prepared which is then tested and verified by the inductive process.* The test may be of observation with naked eye or with the help of microscope but induction and hypothesis are present in both. As far as hypothesis is concerned, it occupies an equal position both in Islamic medicine and in the modern medical science. Both shape their hypothesis with the help of philosophy. The framing of hypothesis is the first step in Islamic research and in this first stage the methods of research in both the Islamic and the modern systems are similar. The basis for this similarity is that in the first stage both require the help of rational sciences (logic and philosophy). After the hypothesis is worked out, the second stage, i.e, induction begins. It is here that the two systems of research, old and modern, differ from each other. In the old system, the process of induction was completed in the light of rational sciences by observation, with naked eye, of the patient while in the modern system of research, the process of induction is completed through microscopic inspection. There are definitely numerous advantages of the microscope. The constituent ingredients of matter can no doubt be understood with a microscope better than by the naked eye. But in the science of treatment, the need to know the potency, the characteristics, the properties and the effects of matter is more important than to know its constituent ingredients. The science of medical treatment is concerned with the efficacy and properties of the matter and not with its constituent ingredients, though in the world of mechanization the constituent ingredients have their importance. The aim of science of medical treatment is not to re-struct the human body but to purge it of the cause of sickness. Therefore, kindly bear in mind that in the science of Tibb, the determination of property, potency and the characteristics of matter are important rather than its constituent ingredients. This object can be better achieved by visual induction under the

guidance of rational sciences. That is, after the drug is administered to a patient its potency, character, effects and properties can be better understood by inspection of the patient on the sick bed. For this purpose visual observation and visual experiment, behind which is a mind trained in rational sciences, will be better. Kindly keep in mind that as the inductive process in Islamic medicine is guided by logic and philosophy, its great advantage is that even those properties of matter can be considered in Islamic medicine which are invisible or out of the microscopic scope. Of these invisible properties are their potency and characteristics. The Islamic medicine therefore determines the temper of each drug on the basis of its characteristics, whereas the modern medical science, since it relies solely on microscopic and chemical analysis which is restricted only to the visibles is bereft of the concept of temper of the drugs.

Another disadvantage of the excessive use of optical instruments in modern medical science is the decline of the mental and deliberative faculties in a majority of modern physicians who tend to rely more and more on mechanical and laboratory tests. This extraordinary dependence has also led to the deprivation, in the modern physicians, of the healing insight which is the distinctive quality of a physician. On the other hand, as the entire asset of traditional medicine is rational sciences and visual observations and inspections, the traditional physicians are fully possessed of such healing insight and understanding.

What more can be said in support of the usefulness of Islamic medicine and its scientific nature than the fact that the modern science whenever it carried out research on herbal drugs of the old, it has only confirmed and verified, and not contradicted or falsified, the effects, characteristics and the indications for use of those drugs as already determined by the classical physicians. By now, research on modern scientific lines has been carried out on as many as 200 old herbal drugs which had been widely used and found beneficial in Islamic medicine and this only brings out into limelight the fact that the old and the modern researchers have the same opinion in respect of the usefulness of the old traditional drugs. The difference, if any, is only of the method of processing and research, the old method being visual and experimental while the modern method is based on microscopic and chemical analysis. The difference in the two methods has resulted in variation in their terminology but has not led to any conflict. Both reflect and interpret the same truth. I present here, for the sake of example, the effects and properties of some drugs as given under Islamic medicine and the result of modern microscopic and chemical research on same drugs whereby you can assess how close are both to each other in the matter of meaning and intent and how modern science has only affirmed and confirmed the usefulness of the old traditional medicines.

Myrtle Berry (حب الأس): A well known and widely used drug in Islamic medicine. The old physicians had determined its temper as cold and dry and had declared it مسكن أمعاء and قابض وحابس الدم. Modern research and chemical analysis has discovered citric acid, salicylic acid, tannin, resin and some fatty constituents. These properties make *Myrtus communis, Linn* sedative, constipating and retarder of bood. All these properties support the effects and properties of this drug as given in Tibb-i-Islami.

WALNUT (الجوز) : According to old research, its temper is hot and dry and it helps to tone up nerves, brain and memory. Modern research and chemical analysis has discovered Vitamins A, B and C in ample quantity in its kernel. In addition important ingredients such as iron, copper, phosphorus, magnesium, arsenic and sulphur have also been found. These ingredients support the effects and properties as determined by Islamic medicine. A thing possessed of so many vitamins and minerals is certainly good for the nerves and the brain.

I may also advert to the startling discovery that the more the scope of research and investigation widens and the more science progresses, the usefulness and efficacy of the old herbal drugs becomes clearer. Till yester years the Western countries had ridiculed the old herbal drugs but as their efficacy is becoming clearer with the advancement of science, the Western researchers themselves are now coming out with information

regarding one or the other herbal drug in Western medical journals. Recently, the Saudi Daily ''Al-Jazira'' by reference to the Western medical journal ''LANCET'' in its edition of 20th October 1985, has made an important disclosure about the usefulness of onion. The daily says: البصل أفضل علاج لمرض السكر .

أكدت أحدث دراسة علمية أن البصل أفضل علاج لمرض السكر حيث أنه يخفض نسبة السكر في الدم ويقلل نسبة الانسولين التي يتعاطاها المريض من عشرين إلى أربعين وحدة يوميا .

(Onion is the most efficacious treatment for a diabetic patient. The latest scientific investigation has proved that onion is the best treatment for diabetes. It helps to reduce the ratio of sugar in blood and thus enables patients whose daily intake of insulin is 20 to 40 to reduce such intake)

A move towards herbal medicines has started in nearly every part of the world. I am now presenting before you the opinion of the Egyptian Doctor Faiza who is professor of Pharmacy in the National Research Centre, Cairo and who is a recognized authority in pharmacology, which can enable you to assess the importance of herbal drugs. The Doctor in the well known Arabic Journal ''Al-Mashriq-ul-Ausat'' which is published simultaneously from London and Jedda, has opined that:

ومع التقدم العلمي اتجه الإنسان إلى الأدوية الكيمياوية وأصبحت نظرته إلى النباتات والأعشاب على أنها أساليب متخلفة إلا أنه مع ازدياد التقدم العلمي ثبت خطأ هذه النظرة وعاد الانسان إلى الطبيعة أعني إلى الأدوية الأعشابية .

(with the advancement of science the attention of man turned to chemical drugs which gave rise to the view that treatment through herbal drugs was out of date and wasteful. But further advancement of science has shown that this notion was erroneous. Now man is reverting to nature, that is, he is returning to herbal drugs).

Further, in the same article, the said Doctor observes that in the Western countries attention has turned to herbal drugs on account of the fact that it has been scientifically established that some modern drugs are cancer causing. He says:

وكان هذا الاتجاه رد فعل لاكتشاف الآثار الجانبية للأدوية الكيمياوية خاصة بعد أن ثبت بشكل مؤكد أن هناك بعض الأدوية الجديدة تسبب الاصابة بالأورام السرطانية .

(Attention to herbal drugs is in fact the reaction of the discovery that chemical drugs are responsible for side effect. Attention to herbal drugs was particularly given when it was established on scientific grounds that some modern drugs are responsible for causing cancer).

Of the many drugs which are becoming responsible for causing cancer, I may draw your attention to one of which the trade name was DES and generic name DIETHYLSTILBESTROL. This drug was administered during pregnancy to prevent bleeding. Since bleeding may lead to abortion, this drug was used to save women from the risk of abortion, but whether it was effective in preventing abortion or not, its use caused cancer among the women expecting to be mothers. The American journal ''Readers Digest'' in its September 1985 issue has given a detailed study of this drug and has called it ''time bomb''. I am sure the same might have come to your notice but I may be permitted to reproduce some extracts from the same:

> ''Over the years it has gradually developed that DES was a ''time-bomb'' drug, exploding years after ingestion in the lives of the children of women who took it''

A sizable number of women fell victim to cancer because of this drug. The reports of research on this drug

which appeared in many European countries showed that a number of women who used this drug became victim of cancer. According to the report of Readers Digest:

> "There have been 25 cases connected with DES in the Netherlands, two of them fatal. In France about 15 cases have been recorded. In Australia at least a dozen case of DES — linked clear cell of adeno-carcinoma have been reported"

It is strange that when a new drug appears in the market, it is hailed by the modern doctors who are full of praise for it but the same drug which had been considered so praiseworthy is, after a few years, discarded and condemned. Not only are the properties and effects of such drugs announced earlier negated and rejected they are found to have various harmful and dangerous effects. In 1940 the drug DES, of which I have just now made a mention and which has been found to be cancer causing, came into the market. It was hailed by the modern physicians and according to the Readers Digest:

> "Almost overnight this synthetic drug was marketed in the United States where it was hailed as a wonder drug and prescribed for millions of women"

According to the Readers Digest, the drug had been invented in 1940 and had been called a wonder drug and had been held to be most effective for preventing abortion. In the early decade of 1950, the researchers reported that the drug was not effective in preventing abortion and, in 1960 it was held to be causing cancer. In 1970 it was reported that the use of the drug had made a number of women in Europe, America and Australia victims of cancer and now in the present decade the drug has been declared dangerous to such an extent that its use can cause cancer not only in the women who take it but also, years later, in their children. It is now called "time bomb drug". It began as a "wonder" drug but has ended as a "time bomb drug". This is unfortunately, the end which the synthetic and chemical drugs come to, and this is the result of our aversion to and escape from nature.

It needs, therefore, to be considered as to what opinion can we have about the system of treatment and drugs about which it is first claimed that they are scientific but then through scientific research it is later discovered that they are harmful and deadly. It is on account of these scientific drugs that the Western countries are now worried about the disasterous effects of their own products.

On the contrary, the drugs of the Islamic medicine even without the aid of microscopic research, are close to nature and on account of this closeness are free from harm and danger. Moreover, their benefits which stand established from times immemorial are now attracting the Western countries. The use of herbal drugs is currently on the increase in most of the developed countries. I may again quote the Egyptian Doctor Faiza to show the importance now assumed by herbal drugs in the developed Western countries:

وقد بدأت كل دول العالم المتقدمة في إجراء البحوث على الأعشاب الطبية واستخراج أدوية منها لعلاج مختلف الأمراض ، ورغم أن انجلترا من الدول المحتفظة جدا في السماح بتداول أي دواء جديد في الأسواق وتضع قيودا صارمة واجراءات دقيقة للتصريح بصناعة دواء جديد وطرحه للاستخدام ورغم كل ذلك فلدى بريطانيا الآن دستور طبي كبير للأدوية من أصل نباتي .

(Many Governments in the developed countries are now turning their attention to herbal drugs and are obtaining medicines for various ailments from herbal drugs. Even in England, which is one of the countries having a conservative and cautious approach, where the use of every new drug is not easily permitted and where there are strict restrictions allowing the use only of such drugs which are permitted only after thorough investigation, a comprehensive organization has been set up for working specially on herbal drugs).

Apart from the scientific nature of Islamic medicine, there is another aspect of its practical and general efficacy which requires consideration. That aspect is the rural character of population of our countries especially the Afro-Asian countries. According to the statistics, 70 to 80 per cent of our population lives in rural areas. From this aspect also you can easily consider how beneficial and unavoidable is the recourse to the Islamic system for the rural population.

For a physician the first stage of treatment is diagnosis of the disease. The physician in the Islamic system is to a great extent self-sufficient in the matter of diagnosis. This is because in acquiring the art of diagnosis he is guided by his training and the rational sciences, in such a way that he is not dependent upon laboratory tests but makes a careful observation of the condition of the patient and the symptoms of the ailment, tries to find a logical connection between the causes and the symptoms of the ailment and thus fulfils the important requirement of diagnosis. For this purpose Islamic system has a regular branch called Science of the General Principles, with the help of which the physician develops a medical insight which helps him to become self-sufficient in the matter of diagnosis and a good deal independent of the need of laboratory tests. You can easily appreciate that in the countryside where means of communication are scarce, where even ordinary dispensaries are non-existent and where radiologists and pathologists are not available, the Western system, which cannot move a step without well-equipped laboratories, cannot work. I, however, leave it to you to compare the two systems and decide as to which of the two systems, the Islamic or the Western, is more suitable, in the national interest, for the rural population of the country.

After diagnosis when we consider the question of nature of treatment (نفس علاج) and nature of medicines (نفس أدوية), the value of Islamic system becomes all the more evident and obvious. Almost 98 or 99 per cent of drugs in this system are herbal which are found mostly in the countryside. This system of treatment, therefore, tends towards self sufficiency in the matter of supply of drugs. There is now an urgent need for reviewing our herbal drugs and subjecting them to research by our scientists so that we not only provide better medicines to our people but also try to become self-sufficient in the matter of their supply.

QUALITY CONTROL OF ISLAMIC MEDICINE

Dr. Inamul Haq

PAKISTAN

Islamic medicine is an ancient form of health care practised long before the appearance of scientific medicine. It is a part of culture of many people and has a very rich heritage. The materia medica of Islamic era was very comprehensive comprising a variety of drugs to combat the various diseases prevalent in those days.

Though the drugs have been used throughout the ages for the treatment of diseases, it was only during the Islamic era that the concept of "Quality" was born for the first time. Besides regular inspections of the apothecary shops by the Government appointed inspectors, the Pharmacists were made responsible to procure, to keep or stock and to dispense sound, genuine and fresh drugs with the main object of providing standard drugs to the consumers. Similarly the first Pharmacopoeia was produced during the Islamic era. Evidently the Islamic medicine duly recognized the importance of using genuine and quality drugs in order to have their full therapeutic effect. The Islamic medicine however met a serious set back under the Western influence because the natural sciences were ignored and stress was laid only on chemistry. With the advent of synthetic drugs during the 19th century, the Islamic medicine went into the background. During the last two decades however there has been a great revival of interest in the Islamic medicine and scientists all over the world are busy in a scientific inquiry into these medicines considering their great therapeutic potential. The Journal of Phytochemistry alone now publishes about 3000 pages annually crammed with reports on natural drugs, all awaiting to be tested for biological activity. Whereas the Islamic medicine is attracting the attention of modern scientists, its quality aspect is being completely ignored and yet Quality Control and standardization of Islamic medicine is imperative to secure uniformity and therapeutic efficacy.

Lately however, there is growing concern about the quality of these drugs apart from their efficacy and safety. What is Quality? Quality of a drug in broad term means that the drug should conform to the established standards and specifications as regard purity, strength and other characteristics during the period of its intended use. So the first and the foremost requirement for standardization of medicines of Tibb is the preparation of Quality Control monographs for each drug laying down their standards and specifications along with methodology for testing.

WHO had published some work on standardization of herbal drugs about a couple of years ago. Similarly PCSIR Laboratory, Peshawar also reported standardization of about hundred herbal drugs. These reports had provided the results of some analytical parameters like ash content, soluble extractable matter etc. of herbs but no attempt was made to estabish the standard and specifications of these herbs against which similar herbs could be standardized. The major constraint in this respect seemed to be the non-availability of authentic specimens of herbal drugs for establishing their standard specifications. Thus the reported attempts of standardization of herbs were of limited value. Before trying to establish specifications of the herbal drugs, the need was however, felt to do some comparative study of the selected herbs already in use in the traditional practice to human the extent of variation between similar species of drugs collected from different parts of the country. It was with this object in view that the National Institute of Health, Islama-

bad started a programme of testing some single herbal drugs which were commonly used by the practitioners of Islamic medicine in their day-to-day practice.

EXPERIMENTAL

Four samples of the same species of drugs representing some leading manufacturers were collected from the four main cities of Pakistan namely Karachi, Lahore, Rawalpindi and Peshawar.

These samples were tested according to the same criteria as laid down in the British Pharmacopoeia for crude drugs i.e. the drugs were subjected to the tests as shown in Table I.

1. Description.
2. Macroscopical characters.
3. Total ash.
4. Acid insoluble ash.
5. Foreign organic matter.
6. Water soluble extractive.
7. Alcohol soluble extractive.
8. Moisture content.

The results were then compiled and it was observed that in the same species of drugs collected from four different localities/places, there were found to be great variations in almost all the parameters tested showing lack of uniformity in their quality. Table II shows the names of the Drugs, studied and the extent of variation in the parameters tested. Evidently any formulation made out of these herbs will show lack of uniformity and quality. However, in the absence of authentic specimens of these herbal drugs it was difficult to say which one was genuine or not.

DISCUSSION

There are around 53000 registered practitioners of Islamic medicine in Pakistan. These practitioners are estimated to be catering about 60% of the population mostly living in the rural areas of the country. They employ either single herbs or mostly compound herbal preparations in their day-to-day practice. Tibbi Pharmacopoeia which is being followed in the traditional practice provides about 900 single herbs and minerals besides including formulation of 550 compound preparations. Another authentic book of recipies followed in traditional practice i.e. "كتاب المجربات" describe about 1250 compound preparations mostly based on herbal drugs. Besides, Hamdard Pharmacopoeia describes innumerable single herbs and compound preparations giving their therapeutic classification.

These drugs are presently being prescribed and used without any quality control checks on scientific lines except perhaps in few cases where some arbitrary standards have been provided. In fact the above quoted sample study has already supported that some of the herbs under study lack quality and uniformity. About a couple of decades ago no such emphasis used to be given to the quality control aspect of herbal drugs and their formulations because in those days such drugs were far and few and they were prepared by or under the supervision and care of healers themselves ensuring their quality to some extent. With the development of herbal drugs trade and industry and also the related technology, these medicines are being manufactured at present on commercial scale necessitating their standardization and quality control on scientific lines.

Though the number of drug manufacturers may run into hundreds there are around ten leading manufacturers of Islamic medicine in Pakistan whose annual turnover is quite substantial and comparable to some big multinational manufacturers of allopathic drugs. They are equipped with some modern facilities for tablet and liquid preparation manufacturing. With the production of these drugs on modern scientific lines

surely there is a need for their quality control on the same lines. As providing standards and specifications for innumerable mostly compound herbal drugs is an extremely difficult task to achieve. Attempt should be made to establish standards and specifications for single herbal drugs to begin with. According to a survey carried out in Pakistan few years ago, there are about 200 herbal drugs most commonly used by the traditional healers in their day-to-day practice. As a first step towards standardization serious efforts should be made to establish specifications for these. For this purpose authentic specimens of these drugs will have to be made available through local sources.

Another problem with the quality of herbal drugs is their contamination with microorganism and pests. The herbal drugs are liable to microbial contamination specially with Pseudomanas sp. Such drugs could prove hazardous to health and needs sterilization. Ethylene oxide gas can be used with advantage for such sterilization under controlled conditions.

But the most effective way of achieving Quality Assurance of Islamic medicine is through the application of certain controls on their manufacture. It is an established fact that the quality of any drug or medicine whether allopathic or herbal cannot be checked or controlled in any analytical laboratory but it has to be built into the product right from the beginning. That was the reason why the concept of Good Manufacturing Practices (G.M.P.) was incorporated into the Drug Legislations of all these countries engaged in the manufacturing of allopathic drugs. In the absence of quality control standards and specifications as well as analytical methodology, the manufacture of Islamic medicine should be subjected to G.M.P. through legislative measures to ensure their quality. G.M.P. includes control on the quality of starting materials i.e. herbal drugs and additives, cleanliness and efficiency of the equipment used in the manufacturing, the quality of the personnel i.e. their qualification, experience, hygienic conditions in the manufacturing area, the effectiveness of the methods of operations etc. So the G.M.P. which lay great emphasis on Men, Machines and Methods can provide good assurances of quality of these medicines.

A phased programme will have to be chalked out to achieve the above objectives.

Short term programme should include:

1. Providing standards and specifications of most commonly used single herbs.
2. Decontamination of herbal drugs before processing and ensuring proper storage conditions.
3. Application of Good Manufacturing Practices on the manufacture of Islamic medicine.

Long term programme should aim at providing standards and specifications for the identity, purity and quality of herbal drugs by developing suitable methodology through the application of modern analytical techniques like chromatography, spectrophotometry etc.

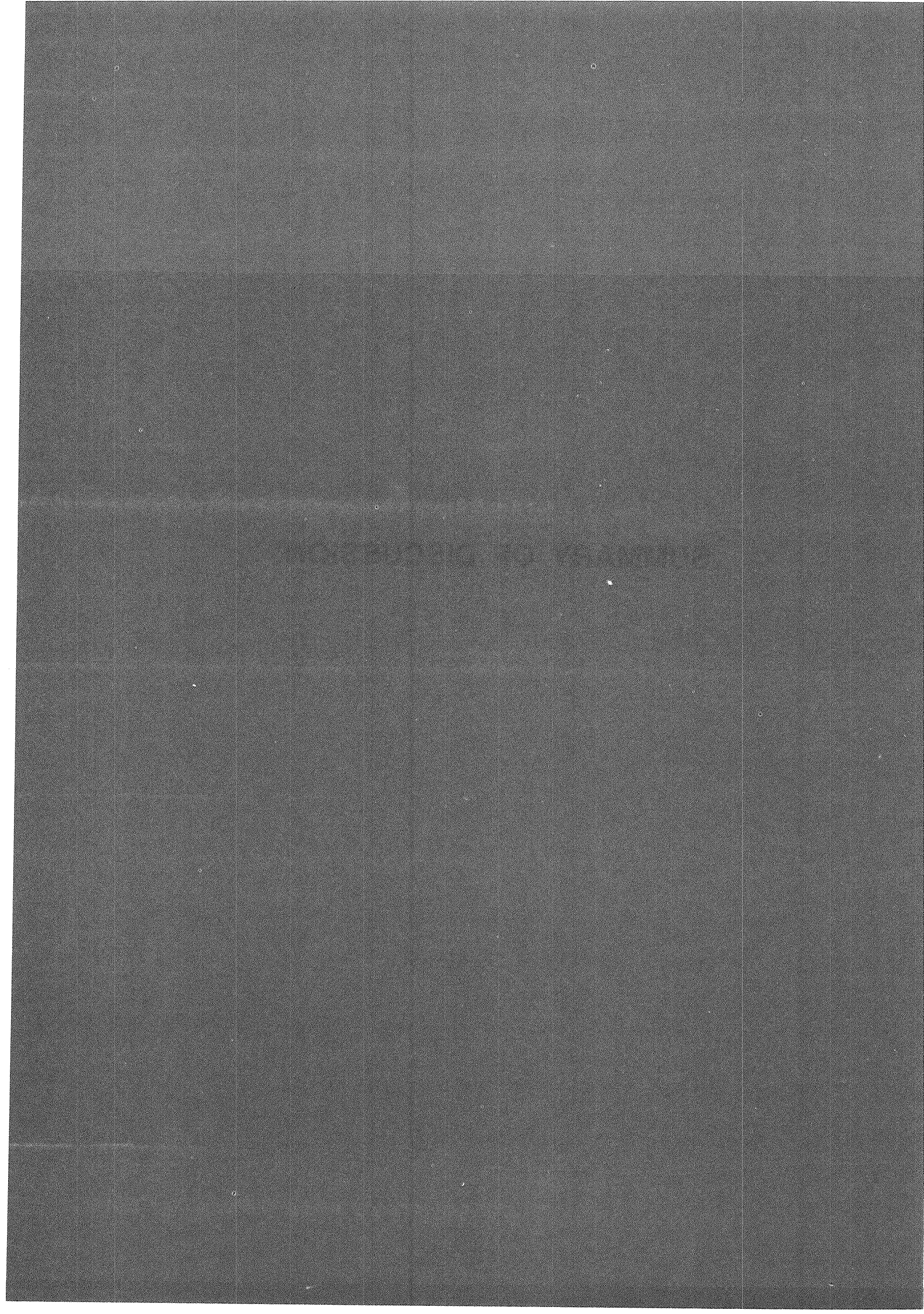
These objectives cannot be achieved without limiting and standardizing the innumerable odd formulations/dosage forms.

The Draft legislation to ensure the efficacy and equality of herbal drugs prepared by the Ministry of Health in Kuwait and the Islamic Organisation for Medical Sciences with the collaboration of EMRO is indeed a valuable document to achieve the above objectives.

CONCLUSION

Since the drugs used in the Islamic medicine may be spurious, adulterated or may not contain genuine species of herbs, there is an urgent need for the control of quality of such drugs so that they may exert their proper therapeutic effect rather than a health hazard. While it is admittedly not possible to lay down standards for all these drugs employed in the Islamic medicine, serious attempts should be made to find some workable standards for the most commonly used important drugs on the lines suggested above to save the consumers from the possible injurious effects of spurious, adulterated or sub-standard drugs.

SUMMARY OF DISCUSSION



Dr. Abdul Fattah Shawki commented: It is high time now that we should not talk about the past, of course without neglecting it, we should talk about the future. The next conference should deal with the future of Islamic medicine. He further pointed out that WHO/UNO has set up a centre in USA about natural products. We should make use of this data bank and we must coordinate our researches with pharmaceutical industry. Now, forty drugs have been mentioned to be produced by genetic engineering.

Dr. Ahmed El-Kadi said, "My objection is about the Islamic medicine terminology; some interpret it as Unani medicine and others as herbal medicine. To me it is a medicine to the total submission to the will of Allah. We still have its restricted use."

Dr. Ahmed Shawki Ibrahim appreciated the paper presented by Dr. Ahmed El-Kadi. He further mentioned "We can not explain that it is the final explanation of Hadith. Therefore, black seed may not necessarily be the blessed seed. Hadith may mean inclusion of thousand varieties of black seeds. We should continue working on herbal medicines."

Dr. Azmat Ansari pointed out that USSR is now condemning the consumption of alcohol and in Scandinavian countries it has been totally banned. Commenting further on Dr. Saleh Jeraiwi's paper, he told that since there are large number of vitiligo patients in Pakistan, Dr. Jeraiwi should guide in the treatment of such patients.

Dr. Sufian M. El-Assouli enquired from Dr. El-Kadi whether the experimental studies on animals would be more fruitful? Dr. El-Kadi commented: "I agree with your idea. There are many people doing active research at many places. However, we do not have an animal house at our Institute".

Dr. Usman Ghani remarking on Prof. Sabir's paper mentioned that Withania somnifera and Pyrethrum indicum are reported to be toxic. How he did not observe any toxic effect with these plants..

Prof. Mohd. Sabir commented: "what I mentioned in my lecture is related to the doses used in our experiments and at those dose levels no toxic effect was observed. Our studies using higher doses are in progress. Moreover, what I mentioned about the toxic effect was specifically related to the observable side toxic effect in relation to gross behavioral changes".

Prof. Dr. M. Abdul Hadi Abu Reeda enquired about the terminology of Islamic medicine. On this question, some discussions generated. He suggested that teaching of Islamic value should be included as part of the curriculum.

Dr. Saleim Ammar while appreciating the paper of Prof. M. Sabir commented that usually the drugs used for antiinflammatory or antiarthritic activities exert ulcerogenic effect and enquired whether the plants used by Prof. Sabir exert such type of action. In response to this enquiry, Prof. Sabir told that the preliminary studies did not show any ulcerogenic effect with the combination of these plants. However, detailed systematic investigations on this aspect was still in progress covering the histopathological investigations on gastric mucosa.

Part Four: *Applied Research: C-Applied Heritage in the field of Medicinal Plants.*

CHAPTER III

SOME SELECTED PAPERS - NOT PRESENTED

1. MASTIC IN TREATMENT OF BENIGN GASTRIC ULCERS
   Dr. Mohammad Jamil Al-Habbal, *et. al.*
2. PLEADING FOR A NATURAL THERAPY
   Dr. Ovidiu Bojor, *et. al.*

MASTIC IN TREATMENT OF BENIGN GASTRIC ULCERS

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and
Dr. Farhad Umer Huwez
IRAQ

INTRODUCTION

Mastic is a resinous exudate from the plant *Pistacia lentiscus* which belongs to the family Anacardiaceae and is cultivated in the Mediterranean countries particularly in the Greecian Archipelago and in the Eagean sea[1].

The chemical composition of Mastic is not similar to any other anti-ulcer drugs because it is composed of resins which constitute more than 90% volatile oil and 2% a bitter principle[2].

Oriental women had used Mastic since long-times as masticatory[3] and as breath sweetener[2].

Mastic is also used it in many parts of Mediterranean and some of European countries as a part of food and flavouring agent in cakes, icecreams, sweets and drinks[4]. In their report on the Review of Flavourings in food (1976), ''Food additives and contaminants committee'' of Ministry of Agriculture (UK), Fisheries and Food — stated that Mastic is acceptable and safe for use in the foodstuffs as a flavouring agent.

Medical uses of Mastic prior to our work on peptic ulcer included:

(1) Temporary filling carious teeth, preserving the teeth and sweetening the breath[5,6].

(2) Compound Mastic Paint — as a protective covering for wounds and to hold gauze in position[5].

(3) It is kept in mouth for sore mouth and cure of aphthae[6].

Since longtimes ago Mastic had been used by the public and local Traditional Healers in many parts of the Mediterranean area for relief of upper abdominal pain and heart burn which probably originated from the Arabic Medicine in the tenth century and afterwards because Mastic had been mentioned by the famous Arab physicians (Ibn Al-Jazzar and Ibn Al-Baytar) for the treatment of gastric ulcers[7,8] and for intestinal ulcers[8].

Recently by using a double blind controlled clinical trial in Arbil Teaching Hospital (North of Iraq), Mastic proved to have statistically significant effect in relieving symptoms and healing of duodenal ulcers over placebo[9]. This prompted us to use it in the treatment of benign gastric ulcer as well. This study was done at Arbil Teaching Hospital.

PATIENTS AND METHODS

Mastic extract was used in the treatment of six patients with benign gastric ulcers which were proved both endoscopically and histologically in an open clinical trial after taking their informed consents. One patient had double gastric ulcers. Two patients did not respond to several months therapy with cimetidine. All the patients

were above 20 years old (five male & one female). The female patient was 70 years old diabetic with ischemic heart disease and atrial fibrillation and she did not respond to several courses of treatment with cimetidine. All other patients had neither clinical nor laboratory evidence of other diseases. They had not received recent treatment within the previous two months with H_2 — blockers, bismuth, carbenoxolone or sucralfate. Mastic extract (in the form of powder) was given in a dose of one gram twice daily (one dose before breakfast and the other at bed time) for four weeks. Routine laboratory investigations including general urine examination and complete hematological and biochemical profiles were done at 0,2 and 4 weeks during the course of the treatment and monthly thereafter for two months after the course of the treatment. Endoscopic follow up was done every two weeks by the same physician (FUH), and the endoscopic findings were recorded on Video tape film. Endoscopic healing was defined as complete epithelisation of the ulcer without appearance of other new ulcers[10]. The patients were told to give up smoking, avoid fried food and anti-inflammatory drugs. They were allowed to take antacid tablets (Gastrigel tablets) on demand for relief of upper abdominal pain. The clinical and laboratory evaluations and followup were done by the other author (MJH).

RESULTS

Complete symptomatic relief was found in all the patients in a mean duration of seven days after commencement of the therapy. Endoscopic healing was found in five patients (including the patient with double gastric ulcers and the elderly female patient) at the end of the four weeks of the treatment with mastic extract.

Neither clinical side effects nor abnormalities in the laboratory indices were observed during the course of the treatment and two months afterwards.

DISCUSSION

The dose of Mastic extract used in this study did not exceed the quantities used by the public as masticatory gum, breath sweetners, or food flavouring. There are no reports of side effects to Mastic, neither from non-medical users, nor in the pharmacognosy books and Encyclopedias of drugs [2,3,5 & 11].

In an earlier doubled blind controlled trial, it was found that Mastic is useful in the treatment of duodenal ulcer and had no side effects[9].

In this report, the number of patients is amall (six cases), because gastric ulcer is not common in Arbil area; 14 cases only (3%) were documented by the authors amongst 463 patients underwent upper G.I.T. endoscopy during one year period[12]. However the observation that all six patients showed symptomatic relief and five of them had complete endoscopic healing at the end of the treatment, suggests that mastic may be useful in treating gastric ulcers. Double blind controlled trails including larger number of patients are planned to see if Mastic can increase the rate of peptic ulcer healing and prevent relapse.

The mechanism of action of Mastic introducing symptomatic relief and ulcer healing is not known. However Mastic is not soluble in water and therefore we raise the possibility that Mastic may form complexes with proteins and produce cytoprotective layer which protect gastric mucosa from injurious agents (such as bile salts and acid pepsin).

More studies are going on to investigate the pharmacodynamics and pharmacokinetics of Mastic to establish its role in the treatment of peptic ulcers.

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PLEADING FOR A NATURAL THERAPY

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and
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If we took a look at our planet from somewhere, not too far away in the outer space, our attention would be first caught by its wonderful greenish-blue colour. In the planetary ocean, on the continental platforms or in the perpetual snow of the polar caps we would see everywhere the marvellous living laboratory: the *vegetable cell.* Life, including ours, would not indeed be possible without that unique laboratory capable of turning the sun, energy and other primary resources into living matter, into organic substances every second.

Biosynthesis provides the existence and comfort of our everyday life: carbohydrates as a power source, hemicelluloses, pectins, benzene nucleus derivatives, lignans, aminoacids a.s.o. as the very basis of biological systems, vitamins, enzymes and phytohormones as essential biocatalysts, tannins, phytosterols, alkaloids, flavones and glycosides as therapeutic agents, essential oils as weapons against the pathogenic germs.

Man-Nature relationship has at present everywhere in the world a distinct significance all the more accentuated by the progress of urbanization and industrialization.

Speaking about industrialization we also have in mind the efforts made to obtain by chemicalization of larger and larger quantities of cereals, vegetables, fruits, meat, eggs, milk, and to obtain or reproduce by synthesis chemical structures with therapeutical virtues.

At present the question is whether our body has been able to adapt itself to the new chemical structures obtained in laboratories after seven decades of excessive industrialization which has included drugs as well. It seems that we can only speak of a partial adaptation since a great number of failures, adverse reactions and side effects have been noticed besides the undeniable therapeutic successes obtained with the synthetic drugs. During the last decades a new pharmacological branch, the drug monitoring system, has been developed as an alarm bell intended to call our attention to the use and abuse of drugs irrespective of their nature. Therapeutic accidents, side effects, toxicity and bioavailability of the natural drugs are however less severe than those of synthetic substances.

On the other hand, the therapeutic concepts of chemotherapy and phytotherapy are completely different. Chemotherapy addresses itself mainly to the affected organ according to the casual allopathic concept while phytotherapy is closer to the homeopathic standpoint having the whole affected organism as a target.

A global concept of phytotherapy is to be found in the old Asian medical systems (Islamic, Ayurvedic, Sidha, Chinese and Unani a.s.o.), as well as in the old Thracian traditional medicine, superior to the classical Greek or Roman systems.

Natural therapy embraces a wide range of remedies starting from food, water, air, natural physical agents

as well as drugs obtained from plants or from inferior and superior animals. Even mineral elements are obtained from secondary resources (as for instance calcium from pearls or egg shells, phosphorus, iron, sodium, potassium, as well as trace minerals from the vegetable kingdom).

In this paper we want to emphasize the preventive and curative importance of phytotherapy, of the therapy based on active substances occurring in the vegetable cell. The natural drug obtained by biosynthesis is indeed easier assimilated by the human body as it is less foreign to the human body. The relationship is quite the same as between a natural and a synthetic or semisynthetic food. The less a food or a drug are processed, the less their natural structure is alterated by means of physical or chemical agents and the better the human organism tolerates them. The food and the medicinal plants contain active or nutritive substances in an ideal ratio to which the human body has adapted itself during its long existence on our planet. Our dependence on the vegetable reign is undeniable; if plants can live without us, we as well as the animals could not survive without plants. Nature has been so programmed on Earth that it may provide us with the primary resources existing on our planet and the sun energy through chlorophyl supplies us with all we need in order to survive and be happy. The closer we shall be to mother Nature, the better we shall understand, know and comply with its unwritten laws the better we shall live.

Coming back to our field, the natural therapy, which embraces on the whole all natural resources starting with the sun rays, the air, the water and ending with deciphering of the genetic code, we shall have to adhere to a unitary view on one of the most wonderful forms of existence: Life. Biology as the science of life covers the most important field of activity on which our own existence will depend. The moment the fossil resources of our planet — supplying the main energy source for industry and technology — are exhausted, we shall have to resort once again to the primary resources that will secure our survival through chloroplasts: that is why scientists from many countries focus their research activity towards a new technical field, the biotechnology, which deals also with the development of new drugs. Using either superior or inferior plants to obtain drugs, synthesis or biosynthesis should always follow analysis, that is a thorough study of the existing structures in Nature. As soon as the pattern is known we shall only have to choose the most convenient way to reproduce the chemical structures we need or to devise new ones as perfect as those provided by Nature. We cannot however estimate how long it will take the living body to adapt itself to chemical structures that do not occur in Nature but are developed by the human intelligence in laboratories.

When in 1805 Sertrüner isolated a pure active substance, morphine, from opium, standardization and preservation of plants and their extracts were considered as settled. Scientists were thinking that only a small number of pure substances from plants were active and all the other chemical compounds were only worthless stuff. One aspect was thus neglected: the active substances from plants represent an active naturally organized complex which owing to some synergic activities have unquestionable advantages over pure substances or over the combinations of active principles. Digitalis is a classical example. After separatiion of pure crystallized cardiac glycosides as digitoxin, gitoxin, gitalin. etc., the remaining substances from Digitalis leaves were considered as a worthless stuff that one had to get rid off. Later on the pharmacological research showed however that the cardiac glycosides are not the only substances responsible for the pharmacodynamic activity of that plant but also the saponins, the calcium salts, the mucosaccharides and other substances existing in Digitalis leaves. We revert thus to the importance of a synergic activity of the principles extracted from plants and to their active, efficient organization following the natural pattern to which the human organism has adapted itself for thousands of years.

During the development of synthetic chemistry, and especially during the first six decades of our century the problem of natural therapy and most particularly of phytotherapy was neglected although a great number of people could not benefit of synthetic drugs and continued using natural remedies as for thousands of years

in the past. What's more, gradually valuable species of medicinal herbs have been taken out of the pharmacopeias of the industrially-developed countries and the plant-based therapy was considered to be merely an adjuvant. This mistaken view lasted until the sixth and the seventh decades of this century, when more and more instances of medicine-induced intoxications, adverse reactions and side effects started occurring, some of them with grave genetic implications on the human body on the human kind as a whole. On the other hand the dropping resources of fossil fuels and industrial raw materials have signalled to researchers, economists and scientists that all these resources are not renewable, that under man's intensive exploitation they cannot last for more than one or two generations. Studies have started once more for a utilization of inexhaustible or renewable energies and raw materials, that is the ones offered by nature.

All these aspects bore a positive influence on the resumption or continuation of research into natural therapies, into the traditional medicine throughout the world. By resorting to a technology superior to that of the past, and to ever finer, more sensitive and adequate methods of investigation, the study of natural remedies — based to a considerable extent on plants and animal products — has witnessed a powerful revival particularly in the industrially developed countries over the last decade.

In the field of phytotherapy the notion of an adjuvant has taken a second position and a classification of the remedies in the field has been made according to the following criteria:

— species of plants, active substances in the plants or the pharmaceuticals made from highly-active plants;

— species with a mild activity;

— species with a weak activity, i.e. adjuvants;

— aromatic species used for preventing or curing infections and parasitic diseases (aromatherapy) or other affections.

On the basis of this classification it may be asserted that in some cases phytotherapy represents the *main treatment* (V.L.B., cardiac glycosides, alkaloids from Rye ergot, alkaloids with tropane nucleus, etc.). The opinion that these remedies are only chemotherapeutic adjuvants must be considered as a false one. We cannot consider as adjuvants the plants with a mild activity or those with a strong activity which are used in high diluted ratios by homeopathy. They represent the basis of long-term treatments necessary in chronic diseases. The active principles of this group are present in several medicinal species belonging to some genus and families unrelated (Chelidonium, Berberis, Leonurus, Valeriana, Anacardiaceae, Compositae, etc.).

As for the species with a weak activity they belong to a very large and varied range of plants such as fruit, vegetables, edible seeds, plantain, lime, country mallow and many others. They can be considered as adjuvants of the basic treatment.

Aromatherapy, another branch of phytotherapy, is suitable especially for the following cases:

— intolerance to antibiotics;

— Infections caused by strains resistant to antibiotics;

— impossibility of performing a surgical treatment because of renal diseases, renal or hepatic lithiasis, parasitic diseases, etc.

We shall end our short pleading for a natural therapy by adding that we cannot exclude synthetic chemotherapy which is very useful in acute, very severe diseases, without suggesting some recommendations which have, in our opinion, a large field of applicability irrespective of the stage reached by different countries.

These recommendations take into account that 80 per cent of the world population use traditional, natural remedies at present and even in the year 2000 a radical change is not contemplated.

Summing up, we think the following trends are necessary if we want the traditional natural therapy to be integrated into the concept of a global therapy:

— a change of the medical syllabus enabling the future doctors to learn other medical systems besides the classical, European so-called scientific system. We think they should study phytotherapy, homeopathy, aromatherapy and apiarian therapy in the first place. Taking into account the progress made in the field of scientific research and the fact that this progress is less known by doctors and not widely applied yet, until new generations of doctors are trained in this field, some specialized training courses should be organized for post-graduates providing information in that field as precise as possible.

— the use of new physico-chemical, biological, biochemical "in vitro" methods to study plants and the pharmaceutical products obtained from them with a view to revaluate the real value of natural remedies and to prove it scientifically. It will be possible to secure a constant, standardized quality of the pharmaceutical products obtained from plants only by using a complex analytic methodology. We insist particularly on the fact that the classical pharmacological methods, particularly those used for the study of allopathic and chemical substances with a strong activity in laboratory animals are not fit to the phytotherapeutical research. Those methods neglect to a great extent the man's specific psychosomatic characters. Finally the most conclusive test is the man's response to the drug and the test of time;

— modernization of mass production of the natural products observing however the traditional methods that have withstood the test of time. A modern technology, a suitable presentation of the natural product should be used in order to ensure a good preservation;

— to offer the patient, under the doctor's guidance, the possibility of choosing between an allopathic, homeopathic or phytotherapeutic drug as the case may be.

We also consider important to thoroughly record and without delay the traditional medicine inheritance from all over the world since any loss in this field is irrecoverable.