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PATHOPHYSIOLOGY OF DIARRHOEA DUE TO GIARDIA LAMBLIA

There seems to be a considerable impact of diarrhoeal diseases on the health of world population. An estimated 3-5 billion cases of diarrhoea are reported each year resulting in 3-5 million deaths per year[1-2]. Despite serious global concern, diarrhoeal diseases are a continuing threat to developing countries, 80 per cent of the deaths in these countries occurring in children below two years of age.

A wide assortment of enteropathogens are incriminated as causative agents of infective diarrhoeas. These are mainly *Vibrio cholerae, Escherichia coli, Shigella* sp. Rotaviruses, *Giardia lamblia, Entamoeba histolytica* and *Cryptosporidium.*

Amongst the parasites causing infective diarrhoeas, there are less prevalent ones also like *Isospora* sp. *Dientamoeba fragiles, Trichuris trichura, Strongyloides stercoralis* and *Ancylostoma duodenale.* However, *G. lamblia* is the most common protozoan parasite of the human intestinal tract and a potential causative agent of diarrhoea. It infects about 2-15 per cent of the population in various parts of the world. In developing countries the incidence is higher, ranging from 5-50 per cent. It is well established that *G. lamblia* is an important cause of significant morbidity, localized water-borne outbreaks of epidemic proportions and traveller's diarrhoea.

There have been major developments over the last decade in our understanding of the biology of *G. lamblia* and pathophysiology of the diarrhoea caused. As late as the mid 1970s there was no universal agreement that this parasite was indeed an important pathogen. This was partly on account of the broad clinical spectrum seen with this infection; ranging from asymptomatic cyst passage to acute or chronic diarrhoea with malabsorption. A multiplicity of signs and symptoms have been associated and a broad spectrum of morphological and functional intestinal changes accompany this infection. Why some patients become acutely ill while others remain virtually asymptomatic needs investigation. Though it is still not fully understood it appears that both the parasite as well as the host factors are responsible for the spectrum of clinical manifestations associated with this infection.

Age seems to be an important pre-disposing factor since children are more susceptible and frequently present with symptomatic giardiasis. Protein calorie malnutrition in the host enhances the susceptibility to infection. Severe malnutrition increases the risk of infection through its deleterious effect on the host's humoral and cellular responses. This decreases the host's ability to resolve the infection thereby increasing the parasite's effect and increased malabsorption. In experimental moderately malnourished mice the parasite causes severe infection as compared to their pair fed controls. However, in severely malnourished mice the number of trophozoites is decreased; possibly due to lack of nutrition. A significant increase in the lymphocyte population of intraepithelium and lamina

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propria in normal and moderately protein deficient animals has been observed. It was ,however, less marked in severely malnourished group[3]. This could be because of severe protein deficiency in this group.

Patients with hypogammaglobulinemia are at increased risk of severe giardiasis characterised by malabsoprtion and chronic abdominal pain[4].

The concept of cooperative action between *G.lamblia* and bacteria, fungi and viruses has been postulated by several investigators[5,6] It is possible that endosymbiosis is responsible for the apparent differences of virulence seen with different *Giardia* strains. Children with giardiasis who require hospitalisation for rehydration have been shown to carry Rotavirus more frequently as compared to other pathogens and this synergistic action might result in symptomatic infection. Proteolytic enzyme activity has been demonstrated in *Giardia*[7]. Two major cysteine proteases of 40 and 50 kDa have been characterised. The 40 kDa protease which cleaves haemoglobin and IgA has been proposed as a virulence determinant. Strain variations also might be responsible for various pathogenesis associated with this infection. Trophozoite counts have been demonstrated to be higher in mice infected with strains isolated from symptomatic patients as compared to those who are asymptomatic. Lymphocyte subset analysis showed an early significant increase in T,B and $CD4^+$ cells and a slight increase in $CD8^+$ cells in animals infected with strains isolated from asymptomatic patients than in those infected with isolates from symptomatic patients[8]. Further, isoenzyme analysis of *G. lamblia* isolates obtained from symptomatic and asymptomatic patients showed phosphoglucomutase (PGM) and hexokinase (HK) enzymes as differentiating markers.

Both luminal as well as mucosal factors are important in the development of diarrhoea and even malabsoprtion in giardiasis. *Giardia* trophozoites consume bile salts *in vitro* by an apparently carrier mediated active transport process[9]. Consumption of host bile salts in chronic infection could theoretically deplete the bile salt pool and thus contribute to the fat malabsorption by impairing the micellar solubilisation of ingested fats and by decreasing the effectiveness of pancreatic lipase. Abnormal pancreatic exocrine function in patients with symptomatic giardiasis has also been reported. Tryptic activity in duodenal aspirates has been noticed to be reduced in infected patients which returned to normal after eradication of the parasite[10]. Stimulated lipase activity is also reduced in infected children and this correlated with fat excretion[11]. Given the large pancreatic functional reserve, the magnitude of the reduction observed in these studies is not itself enough to account for malabsorption but could contribute to a cascade of abnormalities that together impair the absorptive mechanism of the gut to cause diarrhoea with malabsorption.

The mucosal injury inflicted by *Giardia* appears to be the major factor in the pathophysiology of this infection. The earliest suggestion that *Giardia* formed a mechanical barrier to absorption by covering the intestinal surface is no longer acceptable. Some individuals with only a few detectable parasites can have severe symptoms whereas others with massive numbers of parasites may have slight or no symptoms. Moreover effective competition between host and parasite for nutrients would require enormous number of parasites. The large absorptive surface area of the small intestine would seem to compensate readily for such a possibility.

G. lamblia adheres to the epithelial cell surface by means of its ventral adhesive disc. With scanning electron microscopy, several investigations have demonstrated circular marks of various depths left on the microvillous surface by detached trophozoites. These marks were most likely due to alteration/destruction of brush border of microvilli[12]. However, it seems unlikely that this relatively mild destruction of the surface epithelium is sufficient in itself to cause diarrhoea.

Direct association between invasiveness and pathogenesis of *Giardia* infection has been the subject of varied opinions. Electron microscopic studies in animals have shown that mucosal penetration could only occur in areas where necrosis or mechanical trauma was present[13].

Malabsorption of carbohydrates, vitamin B_{12}, D-xylose and vitamin A are frequently observed during *Giardia* infestation. The mechanical barrier mechanism is not sufficient to explain this altered functional physiology of the intestine. It has been reported that during giardiasis the brush border membrane enzymes and transport of monosaccharides and amino acids are reduced[14]. However, uptake of nutrients did not alter significantly with different inoculum size of the organism.

Conflicting reports are available as regards the toxic effects of viable trophozoites or its sonicates. Though no potent toxin has been isolated so far but Nash *et al*[15] isolated and characterised excretory secretory (ES) products of *G. lamblia*. Over 70 per cent of cell surface cysteine rich proteins were released by 24 h into the culture medium. The major ES products released were of 225-94000 molecular weight. Samra *et al*[16] demonstrated that the uptake of

nutrients was decreased in the brush border membrane vesicles treated with ES products. Further, exposure of intestinal tissue to ES products resulted in net secretion of Na^+, Cl^- and 3-0-methyl-D-glucose.

Chen *et al*[17] have reported a CRP gene (CRP136) from *G.duodenalis* which has a repeat sequence homologous to the gene encoding a small class of snake toxins from the burrowing adder—the sarofotoxins.The initial symptoms caused by sarofotoxins *ie* stomach cramps, nausea, vomiting and diarrhoea are similar to those observed in giardiasis infection. It has been suggested that a change in gene regulation of a specific CRP with toxin properties could be the mechanism which changes a non-pathogenic asymptomatic infection to a pathogenic severe giardiasis.

Lectin activity exhibited by *Giardia* merits investigation in the study of toxic mechanisms. Lectins may directly or indirectly contribute to the microvillous damage .Plant lectins are capable of directly damaging enterocytes in animal models. Alternatively lectins may facilitate adherence of the organisms to the mucosa. In *G.lamblia* two distinct lectins have been demonstrated; a 57-78 kDa glucose/mannose specific lectin[18] and a 28-30 kDa mannose-PO_4 specific lectin[19]. Recently Sreenivas *et al*[20] have identified a 148 kDa lectin specific for ∝-methyl-D-mannoside purified from the membrane extract of *G. lamblia.* However, the role of these lectins as potential targets for host immune defences or in facilitating adherence and then producing the pathophysiological alterations in the host remains to be investigated.

An inflammatory response in the lamina propria is frequent in giardiasis. The sensitised lymphocytes in the gut might have an important role to play in the mucosal damage in infected animals. Significant increase in T-cell population of intraepithelial lymphocytes (IEL) and of both T and B cells in lamina propria have been observed by Kanwar *et al*[21].

The rise in the IEL to the same degree as is observed in coeliac disease indicates immunological injury in the form of villous atrophy.Evidence for the role of immune system in producing mucosal injury has been implied from experimental *G.muris* infection in immunodeficient athymic mice. Despite prolongation of infection in these animals, abnormalities of villus architecture were less severe than in immunocompetent mice. When lymphocytes from spleens of immunologically intact mice were injected into athymic infected mice, histological abnormalities developed in the mucosa[22].

In the small intestine, the secretory function is confined to crypt cells while abosrption occurs exclusively in the cells of the villi. With appropriate stimulation, copious intestinal secretion of water and electrolytes may result. The intracellular calcium concentration is a major regulator of transmembrane electrolyte transport. Recently there has been rapid progress in understanding the receptors that generate intracellular signals from inositol lipids. One of these lipids, phosphatidyl inositol 4,5-bisphosphate (PIP_2) is hydrolysed to DAG (diacylglycerol) and inositol triphosphate (IP_3) as part of a signal transduction mechanism for controlling a variety of cellular processes including secretion, metabolism and cell proliferation, *etc.* DAG operates within the plane of the membrane to activate protein kinase C(PKC) whereas IP_3 is released into the cytoplasm to function as second messenger for mobilising intracellular calcium. The activated PKC phosphorylates the membrane proteins thereby altering transport carriers or conductance channel[23].

Though the detailed mechanism of diarrhoea in giardiasis is not fully understood, similar mechanisms involving complex interactions of various biochemical pathways as proposed for other secretory diarrhoeas may be involved.

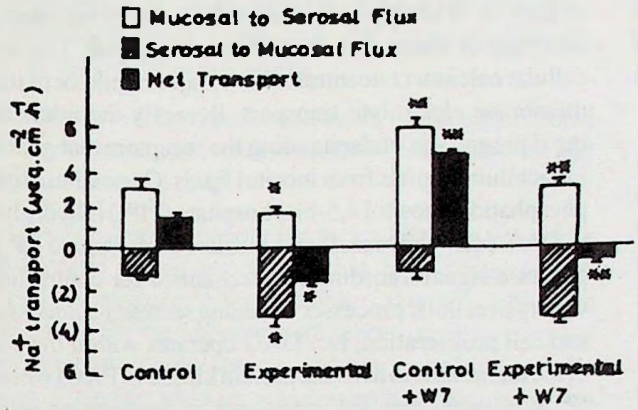
Prostaglandins E and F appear to play an important role, possibly by stimulating the CAMP system. CAMP produces its effect by mobilising Ca^{+2} from intracellular stores which in turn regulates electrolyte transport. PGE/PGF levels have been reported to be higher in infected animals as compared to the controls[24] (Table I).

Table I. Prostaglandins E and F levels in *G. lamblia* infected and uninfected control mice (ng/100 mg of tissue)[24].

Post Infection Day	PGE		PGF	
	Uninfected	Infected	Uninfected	Infected
0	241.12	243.0	32.89	34.12
3	240.33	259.33	33.05	39.33++
6	241.25	288.33**	33.98	53.3*
9	240.98	539.0+	33.12	58.6**
12	242.10	331.66+	33.0	119.66+
15	241.22	321.33+	32.75	84.66+

P*<0.05, **<0.01, +<0.001, ++<0.02
Superscript number refers to the sl.no. in the reference list

Calmodulin, a calcium binding protein, has been shown to be increased in microvillar core during *G. lamblia* infection. Calmodulin decreases Na^+ and Cl^- absorption and leads to hypersecretion. W7 is a specific inhibitor of calmodulin. In control animals with W7 net absorption was observed but in experimental animals already calmodulin was increased and this resulted in net secretion (Fig.1)[25].



*P < 0.01 as compared to control

**P < 0.01 as compared to the same group without W7.

Fig1. Effect of W 7 on Na^+ transport in control and *G.lamblia* infected mice jejunum (Gorowara *et al* 1991).

A two fold increase in intracellular calcium and IP_3 levels was observed in enterocytes isolated from *G. lamblia* infected mice. This causes intestinal ion secretion in *G. lamblia* infection (Table II)[25]. Application of *G. lamblia* trophozoites could bring about a rise in IP_3 levels in mouse enterocytes (Fig.2)[26]. PKC acts in synergism with Ca^{+2} to induce fluid secretion in giardiasis (Table III)[27]. A proposed mechanism of diarrhoea in giardiasis is depicted in Fig.3.

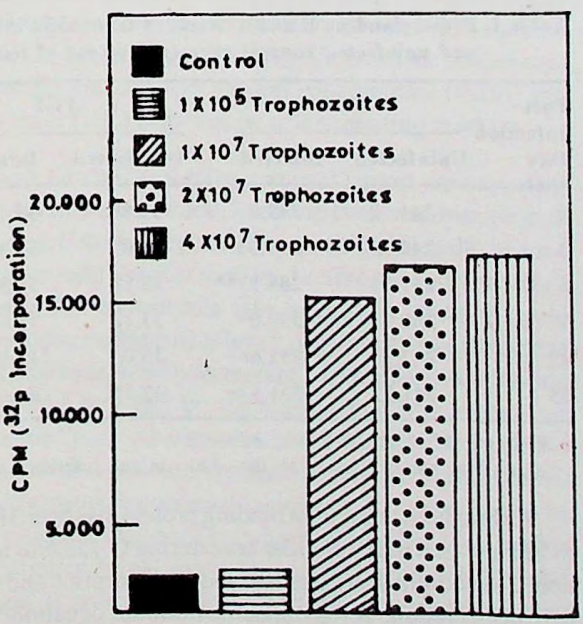


Fig 2. Inositol triphosphate (IP_3) levels in enterocytes treated with *G.lamblia* trophozoites (Gorowara *et al* 1994)

Table II. Intracellular free calcium levels in control and experimental animals[25].

Group	Intracellular free calcium concentration (nmoles/l)
Control	101.150 ± 18.203
Experimental	212.201 ± 10.115*

*P<0.01 as compared to control

Superscript number refers to the sl.no. in the reference list.

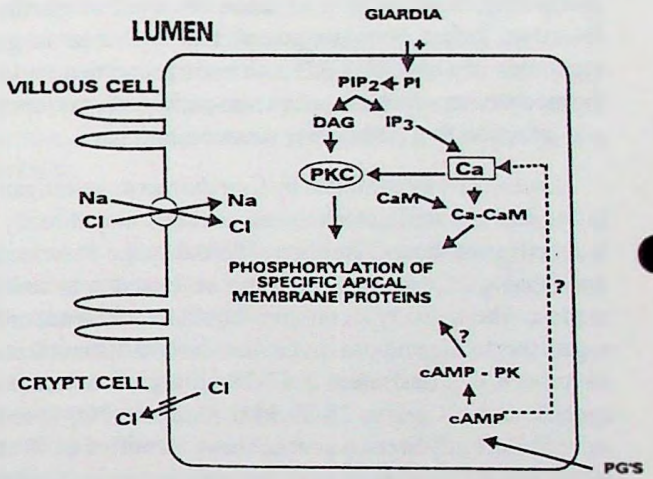


Fig.3. Proposed mechanism of diarrhoea in giardiasis

Table III. Effect of PMA on unidirectional fluxes of Na^+ and Cl^- in the small intestine of control and *G. lamblia* infected animals[27].

Group/Fluxes	Control (μ equiv.cm^{-2}h^{-1})		Experimental (μ equiv.cm^{-2}h^{-1})	
	No addition	PMA	No addition	PMA
Na^+ fluxes				
Mucosal-to-serosal	2.79±0.04	2.70±0.36	1.81±0.21**	1.76±0.19
Serosal-to-mucosal	1.20±0.19*	4.06±0.40	3.40±0.25**	3.37±0.22
Net flux	1.58±0.17*	-1.36±0.14	-1.59±0.19**	-1.61±0.14
Cl^- fluxes				
Mucosal-to-serosal	1.80±0.19	1.60±0.15	1.45±0.20**	1.41±0.21
Serosal-to-mucosal	2.61±0.29*	5.67±0.38	6.48±0.59†	6.58±0.30
Net flux	-0.81±0.07*	-3.99±0.29	-5.03±0.39†	-5.17±0.19

*P<0.01 as compared to the same group with PMA

P**<0.01, † < 0.001 as compared to control

Values are mean ± SE of six determinations

PMA: Phorbol-12-myristate-13-acetate

Superscript number refers to the sl. no. in the reference list.

Much has been learnt about the biology of this parasite in the recent years. It seems likely that *Giardia* causes diarrhoea and malabsorption by a number of mechanism although the relative importance and relevance of each is unclear and incomplete. Further, exploration of the nature of interaction between the parasite and the host factors warrants more information to answer the queries regarding the pathophysiology of giardiasis.

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This write-up has been contributed by Dr. R.C. Mahajan, Department of Parasitology, and Dr. N.K. Ganguly and Dr. H. Sandhu, Department of Experimental Medicine and Biotechnology, Postgraduate Institute of Medical Education and Research, Chandigarh.

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ABSTRACTS

Some Research Projects Completed Recently

Evaluation of the incidence of postoperative pulmonary complications in relation to preoperative status

A total of 836 patients undergoing major surgical procedures were studied to find out the incidence of postoperative pulmonary complications, evaluate the effect of pre-existing lung diseases and other risk factors on the incidence of these complications and compare the incidence of complications under different types of anaesthesia. The effect of efficient postoperative pain relief on incidence of pulmonary complications was also evaluated.

Of the 728 patients who were preoperatively assessed on the basis of history, clinical examination and bedside pulmonary function tests, 516 patients had noraml lung functions while 85, 87 and 40 patients (total 212) had mild, moderate and severe pulmonary disease. Postoperative pulmonary complications developed in 7.69 per cent (56 of the 728) of patients. Pneumonia and atelectasis were the most common postoperative pulmonary complications. The incidence of postoperative pulmonary complications was higher in patients with moderate and severe preoperative lung diseases (26.43 and 37.5% respectively) compared to those with normal lung functions or mild disease (2.9 and 3.5% respectively). The postoperative complications were more frequent in smokers compared to nonsmokers. The incidence was greater following thoracic and upper abdominal surgeries (12.5%) and musculoskeletal and miscellaneous surgeries including operations like hip replacement, thyroidectomy, radicle mastectomy and Harrington-rod insertion for scoliosis (8.75%) compared to those undergoing lower abdominal surgery (2.59%). The incidence was also higher following exposure to general anaesthesia (8.52%) compared to regional anaesthesia (4.54%). Duration of surgery exceeding 4 h was associated with higher incidence of complications; age of the patients had no bearing on the complication rate.

In the second part of the study the effect of efficient postoperative pain relief on the incidence of pulmonary complications was assessed on 108 patients undergoing oesophagectomy. These patients were given analgesia through the epidural route using either a local anaesthetic or narcotics. All these patients were given aggressive preoperative and postoperative breathing exercises and physiotherapy. Fifty five patients receiving conventional opiate analgesia by parenteral route served as controls. The incidence of complications in control group was significantly higher (75.3%) compared to patients receiving epidural anaesthesia (35.29%). This study establishes the role of aggressive chest physiotherapy and breathing exercises in reducing the pulmonary complication rate.

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Publication:

Kaul, H.L., Kashyap, L., Khoshoo, M., Pande, J.N., and Sundaram, K.R. Postoperative pulmonary complications in patients with preoperative lung diseases. *Indian J Med Res 98*: 55, 1993.

Chemical and biological effects of oxygen radicals produced by exposure to benzene and antioxidant potentials in liver and serum during oxidative stress

The efficiency of hydroquinone (HQ) and 1, 2, 4-benzene-triol (BT) iron chelates to act as prooxidants was studied in Wister strain albino rats. Evaluation was done by studying (i) the potential of HQ and BT to release iron from ferritin and whether the iron released could catalyze oxidative reaction; (ii) efficiency of HQ and BT in catalysing bleomycin-dependent DNA degradation, glutathione degradation and lipid peroxidation *in vitro;* and (iii) the antioxidant potentials in serum and liver of rats exposed to benzene.

Administration of benzene consecutively for 10 days to rats of either sex resulted in decrease in antioxidant potentials in serum. Serum uric acid and albumin showed significant decrease in all groups exposed to benzene. α-tocopherol in serum and liver did not exhibit significant change compared to control. Exposure to benzene also led to increase in lipid peroxidation and decrease in free sulph-hydryl groups. Serum ferroxidase activity, total iron content (TIC) and total iron binding capacity (TIBC) measured in female rats exposed to benzene showed significant decrease in ferroxidase activity without any change in TIC or TIBC. The decrease in antioxidation potentials observed may be due to the oxidation reaction exhibited by the benzene metabolites, particularly HQ and BT resulting in oxidative stress in benzene treated rats.

Lower concentrations of BT resulted in the release of iron from ferritin which was able to induce lipid peroxidation and catalyze bleomycin-dependent DNA degradation. The presence of oxyradical scavengers *ie* albumin, catalase or superoxide dismutase significantly

inhibited iron release from ferritin by BT. It was also found that iron complexes with HQ and BT catalyzed bleomycin-dependent degradation of DNA.

Iron catalyzed bleomycin-dependent degradation of DNA was enhanced 12-fold in the presence of glutathionyl hydroquinone (GHQ) and three-fold in the presence of glutathione (GSH). The degradation of DNA was linear with the increase in concentrations of GHQ or GSH, other factors being constant. The presence of oxyradical scavengers *viz* thiourea, mannitol, albumin, superoxide dismutase, catalase and dimethyl sulphoxide caused significant inhibition of degradation by GHQ and iron.

It is concluded that the polyphenolic metabolites of benzene enhance the availability of Fe (II) to bleomycin. Such Fe (II) was possibly made available due to reduction of Fe (III) by polyphenols thus protecting the Fe (II) from hydrolysis to hydroxides and further oxidation. It is also concluded that GHQ is a potent prooxidant, capable of enhancing iron dependent formation of superoxide radical and also due to its faster autooxidation to glutathionyl benzosemiquinone may facilitate formation of adducts with DNA which is one of the prerequisites of benzene toxicity and carcinogenesis.

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ICMR NEWS

The following meetings of various technical committees/groups were held:

Meetings of the Task Forces (TFs)/Project Review Committees (PRCs)/Scientific Advisory Committee (SAC) held at New Delhi:

TF on the study of the normal range of important lymphocyte sub-population in India	March 21, 1997
PRC on Anatomy, Haematology, Human Genetics, Immunology and Physiology	April 1, 1997
TF on the monitoring of adverse drug reactions in India	April 8, 1997
PRC on Pharmacology	April 9, 1997
SAC on Food Contaminants in India	April 10-11, 1997
PRC on Cardiovascular Diseases, Neurology and Mental Health	April 15, 1997

Participation of ICMR Scientists in Scientific Events:

Dr. A. Gajanana, Dy. Director, Centre for Research in Medical Entomology, Madurai, participated in the IV International Symposium on Dengue Fever at Tahiti, Society Island (April 14-17, 1997).

Appointments:

Dr. Kamala Krishnaswamy took over as the Director of the National Institute of Nutrition, Hyderabad w.e.f. April 11, 1997.

Honours/Awards:

Dr. Kalyan Banerjee, Director, National Institute of Virology, Pune, has been awarded the prestigious Shri Om Prakash Bhasin Award for the year 1996 in recognition of his scientific contributions.

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The Regional Occupational Health Centre (Eastern), Calcutta of the Council moved in the new building complex of the Centre at Salt Lake, Calcutta on January 29, 1997.

The Council's Regional Medical Research Centre, Port Blair, moved in the new permanent building of the Centre at Dollygunj on March 29, 1997.

*** *** ***

The ICMR received a generous donation of an endowment from His Majesty Sultan Qaboos Bin Said Al-Said, the Ruler of Oman. His Excellency Mr. Yahaya Bin Mahfudh Al-Mantheri, Minister of Higher Education, Sultanate of Oman, handed over the endowment donation to Director-General, ICMR at a function held at the Institute of Pathology, New Delhi on April 3, 1997.

ICMR AIDED SYMPOSIA/SEMINARS/WORKSHOPS/COURSES/CONFERENCES

Symposium/Seminar/Workshop/ Course/Conference	Date & Place	Contact Address
National Conference of Gerontology and Symposium on Molecular Markers of Aging	April 7-9, 1997; (at Gwalior)	Dr. Y.K. Jaiswal, Organising Secretary of the Conference, School of Studies in Biochemistry, Jiwaji University, Gwalior-474011.
I National Convention of Association for the Promotion of DNA Finger Printing and other DNA Technologies	April 12-13, 1997; (at Hyderabad)	Dr. K.P.C. Gandhi, Organising Secretary of the Convention, Forensic Science Laboratory, Hyderabad-500004.
Training Workshop on Biomedical Communication	June 2-3, 1997; (at Hyderabad)	Dr. C.M. Habeebullah, Director, Decan College of Medical Sciences, Hyderabad-500258.

COUNCIL'S TRAINING PROGRAMMES FOR 1997-98

Leprosy

At the Central JALMA Institute for Leprosy, Agra:

- Training Course on National Leprosy Eradication Programme for Medical Officers (September 15-26, 1997).

Virology

At the National Institute of Virology, Pune:

- Diploma in Medical Virology (July 1997-May 1998).

Reproductive Biology

At the Institute for Research in Reproduction, Mumbai:

- Training Course on Research Methods in Clinical Trials of Newer Contraceptives (April 14-25, 1997).
- Workshop on Genotoxicity (August 28-29, 1997).
- Workshop on Basic Molecular Biology for Clinicians (December 2-11, 1997).

Endocrinology

At the National Institute of Nutrition, Hyderabad:

- Annual Certificate Course on Endocrinological Techniques and their Applications (August 1-September 15, 1997).

Nutrition

At the National Institute of Nutrition, Hyderabad:

- M.Sc. in Applied Nutrition (June 1, 1997-February 28, 1998).
- Postgraduate Certificate Course in Nutrition (December 1, 1997-February 28, 1998).

Occupational Health

At the National Institute of Occupational Health, Ahmedabad:

- Orientation Course on Occupational Health for Industrial Medical Officers (September 30-October 11, 1997).
- Training Course on Environmental Hygiene Practice (November 10-14, 1997).

Laboratory Animal Technology

At the National Centre for Laboratory Animal Science, National Institute of Nutrition, Hyderabad:

- Training Course for Laboratory Animal Technicians (June 16-July 31, 1997).
- Training Course for Laboratory Animal Supervisors (September 1-November 29, 1997).

Haematology

At the Institute of Immunohaematology, Mumbai:

- Training Course in Transfusion Medicine for Blood Bank Medical Officers (August 27-October 24, 1997).
- Training Course in Blood Group Serology and Blood Bank Methodology for Blood Bank Technicians (August 27-September 26, 1997).
- Training Course in Advanced Haematology and Immunohaematology (October 6-24, 1997).

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