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AN OUTLOOK OF CERTAIN OPPORTUNISTIC FUNGI IN INDIA EMERGING AS POTENTIAL HUMAN PATHOGENS

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I am deeply conscious of the great honour done to me by our Indian Botanical Society by unanimously electing me as its President for 1991. I extend my grateful thanks to the Council members of the Society for their courtesy and kindness.

I take this opportunity to express my deep sense of gratitude to my revered teacher, Professor R. N. Tandon, the celebrated mycologist who initiated me to the study of fungi.

On this occasion I remember late Professor Birbal Sahni, the greatest among the great botanists of our country, one of the founder organisers of this Society and former Head of this Department, whose centenary is being aptly celebrated by this University of Lucknow. I pay my umble tributes to him.

I am called upon to deliver at this annual meeting an address as President. I have chosen to talk on "An outlook of certain opportunistic fungi in India emerging as potential human pathogens" for more than one reason. Firstly, I have been interested in this area for the past many years. Secondly, inspite of the increasing importance of this subject to public health, only a very small percentage of mycologists and medical specialists are devoting their research to this field in our country. Finally, this Department of Botany of Lucknow University, the venue of the present Botanical session had been one of the few and pioneer centres of research on medical mycology under the leadership of late Prof. S.N. Das Gupta, former Head of this Department.

The diseases caused by fungi in man are known as mycoses. Mycology which deals with mycoses in man is termed as medical mycology which is also an important speciality in medicine. Raymond Jacques Sabouraud (1864-1936) is considered as the founder of modern medical mycology. Actually he puts medical mycology as a discipline in world sciences. The human pathogenic fungi and their resulting mycoses, which have developed in the last few decades under new environmental conditions, have led to the classification of medical mycology as a well defined and individualized discipline in medical microbiology, alongwith bacteriology, parasitology and virology.

Medical mycology in India was initiated by British medical officers. It was H.V. Carter, a medical officer, who first established in 1860 that a disease of the foot known as Mycetoma or Madura foot, characterised with peculiar swelling, prevalent in South India, was of fungal origin. Similarly the credit of the first report on dermatophyte infection from India goes to Powell (1900) who showed the prevalence of ringworm in Assam. Since then several reviews (Das Gupta *et al.*, 1960; Randhawa *et al.*, 1961; Mohapatra, 1969, 1985; Misra & Sandhu, 1972; and Shome, 1974) have appeared which give an idea of the gradual growing interest and development on researches in medical mycology in India. The studies done so far indicate that superficial mycoses are the most prevalent mycotic infections in our country.

Fungi causing superficial infections affect the keratinized tissue of skin, hairs and nails of man and animals. Universally recognised etiologic agents of such infections are species of *Trichophyton, Microsporum* and *Epidermophyton* (the dermatophytes).

In recent years there has been an increasing number of reports concerning human infections by fungi other than the dermatophytes or the recognised pathogens. The fungi involved are normally common free living saprobes. Such opportunistic fungal infections are emerging as a relatively new area in medical mycology. With the introduction of steroid therapy, cytotoxic drugs for treatment of malignancies, immunosuppressants in transplant patients and several broad spectrum antibiotics, more and more cases of infections, many of which may be unusual diseases of clinical rarity, due to opportunistic fungi, wide spread in nature are being reported. It is clear

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that great many fungi, provided that they can gain access to human tissues, do not find the body a milieu inimical to their growth (Emmons, 1960).

Now let us look at some opportunistic human fungal infections like candidiasis, aspergillosis, zygomycosis, phaeohyphomycosis, chromoblastomycosis, hyalohyphomycosis, onychomycosis and keratomycosis.

CANDIDIASIS

It is a primary or secondary mycotic infection caused by members of the genus *Candida*. The clinical manifestations may be localized to the mouth, throat, skin, scalp, vagina, fingers, nails, bronchi, lungs or the gastro-intestinal tract or become systemic as in septicaemia, endocarditis, and meningitis. Its distribution is worldwide, the most common and frequently encountered species of *Candida* is *C. albicans*. Under normal conditions it appears to be an obligate neutral since it has rarely been isolated from soil or other non animal substrates, and there is no evidence that it can grow successfully in such habitats. It may be significant in this respect that inocula of *C. albicans* are transmitted from animal to animal or man and are not derived from other sources.

Normally, penetration of even the superficial layers of the body does not take place, but a change in the physiological status of the host (i.e. man) may result in invasion giving rise to candidiasis. Predisposition of the body to invasion may be brought about by a number of natural and unnatural factors such as moisture, hormonal influences, age, general debility, interference with immunity mechanism, interference with normal bacterial flora and mechanical factors.

Superficial candidiasis with various mucous and cutaneous manifestations is now the most common cutaneous mycosis. The various oral, cutaneous and even allergic manifestations are now well described. Their incidence has increased considerably since the introduction of antibacterial therapy (Odds, 1988). Thus, an important opportunistic marker in AIDS patients (Klein *et al.*, 1984; Tavitian *et al.*, 1986), is a clinical manifestation due exclusively to *C. albicans*.

Shastry *et al.* (1969) monitored the hospitalised patients put on broad spectrum antibiotics and demonstrated a higher percentage of them harbouring *C. albicans* as a consequence. *C. albicans* is reported to be fairly common in patients with chronic respiratory diseases, particularly patients undergoing prolonged antibiotic therapy. Sandhu *et al.* (1979) and Mehta & Sandhu (1988) have reported the aetiological role of *C. albicans* in several cases of allergic bronchopulmonary mycoses from Amritsar and Delhi. Interesting information as to the parasitic and saprophytic association of *C. albicans* and related species has been well worked out (Chakravarty & Sandhu, 1962; Sandhu *et al.*, 1962; Grover & Junnarkar, 1965; Dastidar *et al.*, 1966) showing about 40-50% incidence of *Candida* in patients of bronchopulmonary disorder (Shome, 1974).

The other forms of candidiasis can be produced by various other *Candida* species like *C. tropicalis, C. krusei, C. parapsilosis, C. guilliermondii* and *C. pseudotropicalis*. Mohapatra (1985) reported that *C. paronychia* and *C. vulvovaginitis* are the commonest manifestations in the patients attending the out patient services in the pediatric, dermatology and obstetrics and gynaecology departments. *C. viswanathii* has been isolated from the cerebrospinal fluid of a fatal case of meningitis from South India (Viswanathan & Randhawa, 1959; Sandhu & Randhawa, 1962). Sandhu (1970) has isolated *C. viswanathii* from another fatal case of meningitis from varanasi while the patient was still living. These findings point to the possible wide occurrence of *C. viswanathii* in India with its potentialities to cause meningitis in man (Mishra & Sandhu, 1972).

Recently Fromtling *et al.* (1987) reported that *C. tropicalis* has emerged as a potential dangerous opportunistic fungus. This species has been found to be involved world over as a frequent opportunistic pathogen in a variety of infections including pyelonephritis, UT infections, arthritis, meningitis and pericotitis. Singh *et al.* (1992) reported a case of systemic bronchopulmonary disorder from Jabalpur caused by *C. tropicalis* for the first time. However, in many of these reports the most important criterion of histological demonstration of the tissue invasion by *Candida* has been omitted, may be because it is not easily practicable in most cases. Singh *et al.* (1992) though could not demonstrate histopathological evidence, depended on the following reliable evidences for their diagnosis, repeated isolation of *C. tropicalis* from sputum, bronchial aspirate, urine, peripheral blood of the patient; its pathogenicity on

the mice, its proteolytic activity and absence of acid fast bacillus.

Several species of *Candida* are now being increasingly recognised as potential pathogens, particularly in the compromised hosts. More attention is required to be paid to this cosmopolitan opportunistic dangerous fungal invader.

ASPERGILLOSIS

Aspergillosis caused by species of *Aspergillus* can be easily labelled as the most hazardous opportunistic infection of patients whose body defences are impaired.

Aspergillosis is a spectrum of diseases of humans and animals caused by members of the genus *Aspergillus*. These include (1) mycotoxicosis due to ingestion of contaminated foods; (2) allergy and sequelae to the presence of conidia or transient growth of the organism in body orifices; (3) colonization without extension in preformed cavities and debilitated tissues; (4) invasive, inflammatory, granualomatous, necrotizing disease of lungs, and other organs; and rarely (5) systemic and fatal disseminated disease. The type of disease and severity depends upon the physiologic state of the host and the species of *Aspergillus* involved.

Aspergillus is worldwide in distribution. Among the large number of saprophytic species of *Aspergillus* common in our environment, *A. funmigatus, A. flavus, A. niger, A. nidulans* and *A. terreus* are known to cause disease in man.

The systemic infection with *Aspergillus* particularly with *A. fumigatus* is now well recognized as an opportunistic infection. A preexisting cavity in the lung is a suitable site for this fungus to grow. The use of immunosuppressants and other cytotoxic drugs also predispose to this infection. Among the bronchopulmonary aspergillosis, the commonest entity is the formation of a fungus ball, 'aspergilloma', in the lung cavity due to the growth of the *Aspergillus*.

Bronchopulmonary aspergillosis has been reported from different parts of our country from time to time. Gupta & Viswanathan (1963), Reddy *et al.* (1965), Sandhu *et al.* (1966), Chitnis & Deshpande (1967) and Misra (1971) have reported cases of aspergilloma. Allergic aspergillosis has been reported by Misra (1971), Sandhu *et al.* (1972), Sandhu & Sandhu (1973), Shome (1973), Khan *et al.* (1976, 1977), Sandhu *et al.* (1979) and Mehta & Sandhu (1988).

A. fumigatus (the main etiologic agent of bronchopulmonary aspergillosis) is a thermotolerant species possessing relatively smaller size conidia and hence better adapted for deeper penetration and survival in the lungs. This coupled with its known allerginicity account for its prominent etiological role in allergic bronchopulmonary aspergillosis (ABPA) (Mehta & Sandhu, 1988).

Lesions of the central nervous system due to *Aspergillus* have been reported in literature, though rarely. Bannerjee *et al.* (1977) reported from Chandigarh rather some unusual cases of cerebral aspergillosis. Cases of granuloma of the brain have been detected at the All India Institute of Medical Sciences, Delhi and at the Neurology Institute, Madras (Mohapatra, 1985). A case of *Aspergillus* granuloma of maxillary sinus caused by *A flavus* was reported by Arora *et al.* (1979) from Rohtak. However, cases of granuloma of the brain deserve special attention with regard to the confirmation of the etiologic role of *Aspergillus* by culture and species identification.

Naidu *et al.* (1991) have for the first time documented *Aspergillus chevalieri* as opportunistic pathogen of human cutaneous aspergillosis from Jabalpur. They have presented evidence that *A. chevalieri* is a potential pathogen of mammals and that GI tract could be an important portal of entry for this fungus in to the host tissue. Therefore, isolation of *A. chevalieri* from the clinical sample of any immunocompromised host should be viewed cautiously by the clinicians.

ZYGOMYCOSIS (MUCROMYCOSIS OR PHYCOMYCOSIS)

Zygomycosis is a term given for convenience to a group of mycoses caused by commonly occurring species of the genera of zygomycetes.

An acute and rapidly developing, less commonly chronic, infection of debilitated patients. Depending on the portal of entry, the disease involves the rhino-facial-cranial area, lungs, gastrointestinal tract, skin or less commonly other organ systems. The infecting fungi have a predilection for invading vessels of the arterial system, causing embolization and subsequent necrosis of surrounding tissue. A suppurative, pyrogenic reaction is elicited; gra-

nuloma formation is not frequently encountered.

The disease is world wide in distribution. The common etiologic agents are cosmopolitan members of the Mucorales including species of *Rhizopus, Mucor, Rhizomucor, Absidia, Cunninghamella, Saksenaea* and *Mortierella*.

There are only few reports of zygomycosis from India, specially the systemic or deep seated infections. Balasubramanyam & Chaudhuri (1963) reported a fatal case of pulmonary mucromycosis in a 5 year old male child who apparently died of high fever.

Grover *et al.* (1966) have reported a case of cerebral mucromycosis in a 16 year old diabetic male patient who had developed an ulcer over forehead and scalp for about a month and had suffered from drowsiness and high fever for 8 days. The condition of the patient after admission deteriorated fast leading to death before any therapeutic measures could be taken. At autopsy small areas of necrosis were noticed in the left frontoparietal region of the brain. Investigations revealed the presence of *Rhizopus oryzae*.

Madhavan & Reddy (1969) reported a case of mucromycosis of intestine. Nonseptate pleomorphic hyphae were seen in the histopathological sections of the intestines.

Kamalam & Thambiah (1980) reported for the first time a case of human cutaneous infection caused by *Syncephalastrum* sp, which is considered as a soil saprobe.

Saksenaea vasiformis was for the first time reported from the soils of Sagar by Saksena (1953) and was classified as a member of Zygomycetes. Thereafter there have been several reports about its occurrence throughout the world. The first human infection due to *S. vasiformis* was reported by Ajello *et al.* (1976). Since then only 12 cases have been reported so far from all over the world.

In India Padhye *et al.* (1988) for the first time reported a case of subcutaneous zygomycosis caused by *S. vasiformis*. However, no case is known of systemic mycosis caused by this fungus in India.

Inspite of the fact that there are only very few reports on zygomycoses, the potential danger from them is a constant threat to the population in our country.

PHAEOHYPHOMYCOSIS

This term was coined by Ajello (1974). It is a mycotic infection of humans and lower animals caused by a number of dematiaceous (brown pigmented) fungi where the tissue morphology of the causative organism is mycelial. This separates it form other clinical types of disease involving brown pigmented fungi where the tissue morphology of the organism is a grain (mycotic mycetoma) or sclerotic body (chromoblastomycosis). Clinical forms of the disease range from localized superficial infections of the stratum corneum (tinea nigra) to subcutaneous cysts (phaeomycotic cyst) to invasion of the brain.

Human infections by dematiaceous fungi have been observed with increasing frequency during the past few years. This has been due to the recognition of the fact that several fungi which were usually considered saprophytes or plant parasites have the potential to infect man.

The earliest known case of subcutaneous phaeohyphomycosis in India was reported by Rajam *et al.* (1958) caused by *Hormodendrum dermatitides* which was later reidentified as *Exophiala spinifera* by Padhye *et al.* (1984). Bagchi *et al.* (1962) reported a case of uncommon brain tumour caused by *Cladosporium trichoides*. Desai *et al.* (1966) also reported a case of brain mycosis in which *Cladosporium trichoides* was implicated. Wadhwani & Srivastava (1985) reported two cases of nail infection caused by *Alternaria humicola* and *A. pleuriseptata*. Recently Khan *et al.* (1988) demonstrated the repeated occurrence of *Sporotrichum pruinosum* in the respiratory tract of 3 patients suffering from respiratory disorders. They found that the fungus was able to incite lesions in experimentally infected mice, thus supporting an etiologic relationship. Singh *et al.* (1992) reported *Sporotrichum pruinosum* and *Cladosporium oxysporum* to be associated with bronchopulmonary disorders in an old lady at Jabalpur. However, histopathological evidences could not be demonstrated, perhaps it was not possible, Singh *et al.* (1992, 1990) also reported *Exophiala jeanselmei* var. *laconii* and *Alternaria chlamydospora* causing skin infection in man for the first time from India. They observed that *A. chlamydospora* has emerged as a highly potential opportunistic fungal pathogen. Prevalence and distribution of cases of *A. chlamydospora* need further investigations. Singh *et al.*

(1991) have newly reported *Phialophora richardsiae* from Jabalpur causing phaeohyphomycosis. This organism is known to cause phaeohyphomycotic cyst but interestingly they have observed it to cause skin lesions without cyst. *Bipolaris australiensis, B. hawaiiensis, Cochliobolus hawaiiensis, C. sativus, Curvularia senegalensis, Cladosporium sphaerospermum, Gloeomastrix murorum* and *Chaetomium* sp. have also been newly observed by Singh (unpublished) causing cutaneous phaeohyphomycosis.

CHROMOBLASTOMYCOSIS

It is a mycotic infection of the cutaneous and subcutaneous tissues characterised by the development in tissue of dematiaceous, muriform, rounded sclerotic bodies. Infections are caused by the traumatic implantation of fungal elements in to the skin and are chronic, slowly progressive and localized. Tissue proliferation usually occurs around the area of inoculation producing crusted, verrucose and wart like lesions. It is world wide in distribution but more common in bare footed populations living in tropical regions. The etiologic agents are various dematiaceous hyphomycetes associated with decaying vegetation or soil especially *Phialophora verrucosa, Fonsecaea pedrosoi, F. compacta* and *Cladosporium carrionii.*

In India chromoblastomycosis was for the first time recognized by Kakoti & Dey (1957) in Assam in a female patient involving her external genitalia with metastasis in the inguinal lymph nodes. The causal agent was identified as *Hormodendrum compactum* now known as *Fonsecaea compacta.* Several cases of chromoblastomycosis have been described from Andhra Pradesh (Radhakrishnamurty, 1981).

HYALOHYPHOMYCOSIS

The term hyalohyphomycosis was introduced by Ajello in 1982. These are infections similar to phaeohyphomycosis but caused by hyaline fungi. In vivo such fungi form hyaline mycelium. Commonly met aetiologic agents of hyalohyphomycosis are *Fusarium* species, particularly *F. solani* and *F. oxysporum, Paecilomyces lilacinus,* and *P. variotii* etc.

Fusarium species are known to be soil saprophytes or plant pathogens, but have been reported to cause human infections from several countries and are responsible for many diseases viz. ulcerated leg (English, 1972; English *et al.,* 1971), burn lesions (Holzegel & Kempf, 1964), necrotic skin (English, 1968), subcutaneous granuloma (Attapattu & Anandkrishnan, 1986), and facial granuloma (Ronald *et al.,* 1970). In rare instances it forms brain abscess (Steinberg *et al.,* 1983) and a disseminated infection with vascular invasion (Okuda *et al.,* 1987).

However, reports on *Fusarium* infections in India are not common. There is no reason that they should be uncommon in our country but perhaps such infections have not been discovered. Some cases of hyalohyphomycosis have been newly reported from Jabalpur. Barde & Singh (1982) reported infection of nail by *F. solani* and *F. oxysporum.* Cutaneous hyalohyphomycosis due to *Paecilomyces variotii* has been reported by Naidu & Singh (1992). *Penicillium chermisinum* has also been found to cause cutaneous lesions at Jabalpur (Singh, unpublished).

ONYCHOMYCOSIS

Onychomycosis means infection of nail apparatus by fungi. It is caused by three groups of fungi - dermatophytes, nondermatophytes (moulds) and yeasts (English, 1976). Several nondermatophytic fungi have been implicated in nail disorder (Ramesh *et al.,* 1980; Puri *et al.,* 1978; Singh & Barde, 1980, 1983, 1986; Wadhwani & Srivastava, 1985). It is now well recognized that some nondermatophytes are capable of invading nail tissue particularly after damage due to trauma or disease with the exception of *Hendersonula toruloidea* and *Scopulariopsis brevicaulis* which are considered true invaders. Agarwal & Singh (1980) for the first time implicated *Microascus cinereus* in the human nail infection from Jabalpur. Later on Singh & Barde (1990) also revealed three cases of onychomycosis caused by *M. cinereus* from Balaghat (M.P.). Naidu *et al.* (1991a) have documented the first instance of opportunistic onychomycosis caused by *Chaetomium globosum* from Jabalpur. Naidu *et al.* (1991b) have also reported a case of nail infection by *Scopulariopsis brumptii* for the first time. Besides these, *Curvularia lunata, Phialophora bubakii, Cladosporium carrionii,* and *Aspergillus* sp. have also been implicated for the first time in nail infection from Madhya Pradesh (Singh & Barde, 1986, 1990).

KERATOMYCOSIS (OR MYCOTIC KERATITIS)

It is an opportunistic fungal infection of the eyes that usually causes ulceration, suppuration and in-

flammation usually following trauma to the cornea by vegetative matter, soil or surgery. Prolonged treatment with corticosteroids may also be a predisposing factor. It is ranked behind the major blinding diseases of eyes in the tropics such as cataract or trachoma. Mycotic corneal ulcer is one such corneal disorder which, if not suitably treated, could result in serious ocular morbidity or even blindness.

A review on keratomycosis has been published by Sandhu & Rattan (1980). In recent years more and more saprophytic fungi present in our environment are being reported as opportunistic causal agents of mycotic keratitis. In India, several studies have shown mycotic keratitis to account for 15 to 35 percent of cases of corneal ulceration (Sood *et al.*, 1968; Reddy *et al.*, 1972; Kulshrestha *et al.*, 1973; Das Gupta *et al.*, 1973; Srivastava *et al.*, 1975; Sharma, 1988). However, several of the published reports have not been well documented with regard to the identification of the causal agents.

Shukla *et al.* (1983) reported for the first time two cases of keratitis caused by *Colletotrichum* state of *Glomerella cingulata* and *Acrophialophora fusispora*. Rajasekaran *et al.* (1986) have reported *Fusarium*, *Aspergillus flavus*, *A. fumigatus*, *Penicillium* sp., *Curvularia* sp., *Helminthosporium*, *Alternaria* sp., *Cladosporium* sp., *Mucor* sp., and *Trichosporon* associated with keratitis from Trichuirapalli (South India). Shukla *et al.* (1989) have implicated *Phaeotrichoconis crotolariae* for the first time with mycotic keratitis from Lucknow. Most workers in India have reported various speicies of *Aspergillus*, especially *A. fumigatus*, *A. flavus* and *A. niger* as the commonest isolates in mycotic keratitis (Thomas *et al.*, 1986). However, Sharma (1988) and Singh *et al.* (1990) found *A. terreus* to be the most prevalent aetiologic agent at Jabalpur. Other species found to be associated with mycotic keratitis at Jabalpur include *Fusarium solani*, *Cylindrocarpon tonkenensis*, *Alternaria alternata*, *Cladosporium sphaerospermum*, *Candida albicans* and *Aspergillus fumigatus*.

Although during the last 30 years or so several reports from different parts of the country have appeared indicating a better awareness of the disease, however, laboratory diagnosis of keratomycosis is not so far readily available. Moreover, the causal fungi being common saprobes, their etiological role is not easy to establish. Our knowledge of various aspects of pathogenesis of corneal ulcer is inadequate particularly in relation to the role that fungal toxins or enzymes might be playing in tissue destruction and the immunological processes involved. Besides, the therapy of fungal infections do not always produce satisfactory results.

The clinical manifestations of fungal corneal ulcer vary depending upon the type of causal agent, degree of invasion, presence of mycotoxins and the resistance of the host etc. Nevertheless, a typical mycotic corneal ulcer starts as a fluffy white spot with a severe ocular reaction, fungal hyphae and endothelial plaque of white material being visualised around the margin of ulcer, and hypopyon is common. Thomas (1989) stated that in histopathological sections of the cornea the fungi are located at a deep level and are absent on the surface.

Sharma (1998) at Jabalpur for the first time attempted to determine the ecological niche of such fungi which cause mycotic keratitis. She successfully used goat's cornea as the selective bait in the isolation of fungi from the environment. Such a study employing mammalin cornea can be of much help in the preparation of regionwise list of opportunistic ocular fungal pathogens. The fungi implicated in mycotic keratitis so far, in a vast country like India, are only representative of the large mycological flora existing here.

Mycotic keratitis is still being neglected even at the international level, particularly in the third world countries where many people are losing their vision due to lack of proper understanding and management of this disease.

EPILOGUE

It is evident that fungal human pathogens are of great importance to public health and their prevalence in our country may be far more than our current estimation. If fact, the true dimensions of medical mycological problems in India are not yet fully known. There is the need for an extensive survey throughout the country to reveal the true picture of mycoses regarding their incidence, prevalence and information on morbidity and mortality. It has been experienced that a large number of cases with ulcers, abscesses, swellings, tumours and respiratory disorders of mycotic etiology are often misdiagnosed as

other infections or sometimes as malignant lesions.

The problems connected with ecology and epidemiology of mycoses deserve more attention because inter-human relationships constitute the prime factors that explain the presence or absence of the infections.

In fact very little is known in the area of fungal pathogenesis. It is an area that must be examined in greater depth.

For a better understanding of human fungal infections much work is needed on various aspects like epidemiological, clinical, pathological, immunological and mycological, which can be possible only through interdisciplinary collaborative research between clinicians and mycologists.

The frequency and severity of fungal infections in man specially in immunocompromised hosts have necessiated intensive research in the development of new antifungal drugs and new strategies for their control.

Plants have been the source of medicines for various human ailments including skin diseases. Therefore, attempts to develop antifungal drugs also from indigenously available plants besides chemicals and antibiotics will be worthwhile because such drugs may prove more safe, effective and economical.

I take pleasure in expressing my grateful thanks to my pupil and research associate, Dr. S.M. Singh, Professor of Bioscience, R.D. University, Jabalpur for discussions and help in the preparation of this address.

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