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"THE NATURAL COURSE OF CHRONIC DISEASE" **

by

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A disturbing feature of medicine in the current situation is the multiplicity of drugs available for the cure or relief of diseases. Forty years ago, there were no antibiotics, steroid harmones, antihistamines, hypotensives, tranquilisers, relaxants. The present period is called the antibiotic era, soon to be followed by the atomic era. Inspite of the spectacular therapeutic advances wrought by the advent of the antibiotics, vociferously publicised in lay and medical press and by a never ending plethora of advertisements and high pressure salesmanship there are shadows discernible in the current use of the antibiotics. We are living in an era of promiscuous therapeutics in which treatment precedes diagnosis. Antibiotics are prescribed, widely, indiscriminately and thoughtlessly to all and sundry conditions for many of which there are no indications. The erstwhile innocuous penicillin has become the most potent sensitizer with often fatal reactions. I have it on good authority that Streptomycin is being prescribed by certain physicians for every patient who is found to be Mantoux positive.

Apart from the allergic and non-allergic complications of antibiotic therapy, there is increasing evidence of a subtle change in the pattern of many diseases, and the occurrence of new diseases syndromes with often times serious metabolic, ecological and immunological alterations in the human organism. The latter have been aptly termed Iatrogenic diseases. A few examples may be given. Systemic fatal moniliasis, and acute fulminating staphylococcal enteritis following antibiotic therapy have been reported. Serious staphylococcal infections of the throat, skin and bones due to the emergence of antibiotic resistant organisms have been increasingly encountered both in hospital and private practice. Tuberculosis till recently was considered a killing disease; with the advent of antibiotics while the mortality from the disease has, registered a significant decline, the morbidity figures

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do not show any such desirable result. According to some thoughtful physicians, antibiotics may merely convert a killing disease into a crippling one. The problems of antibiotic resistance and antibiotic dependence are looming ahead to confound the physicians and microbiologists. During the past decade, in America and Western Europe, symptomatic syphilis has shown a rapid decline while latent syphilis is showing an upward trend. Is it a case of syphilis going underground beneath the threshhold of clinical recognition due to the widespread use of Penicillin ? Time and further observations alone can tell. In our country, although organised efforts at syphilis control are lacking, there is some evidence that the hospital admissions for early symptomatic syphilis have registered a decline during the past few years. This decline may be due to two causes, (*a*) Increasing use of penicillin among the population for conditions other than syphilis. Such 'happenstance' treatment may prevent or abort an unrecognise syphilitic infection. (*b*) The reduction in the hospital admissions for early syphilis may be due to an increasing number of patients with the disease seeking treatment from private physicians.

According to Magnuson another factor of importance in bringing penicillin by chance to the unrecognised syphilitic is gonorrhoea. In Western countries it is stated that the incidence of Gonorrhoea has not shown any significant decline and this may be a factor in lowering the syphilis attack rate, through administration of penicillin for Gonorrhoea to a large number of persons of these socio-economic groups of the population where syphilis is most rampant. Schamberg in a thoughtful speculative article poses and answers the question 'Can the Treponeme stage a comeback?' She offers the possible explanation for the failure of Gonorrhoea to decrease comparable to the decline of syphilis in America and other Western Countries, to the shorter incubation period of Gonorrhoea in men. If the incubation period of syphilis is taken as 2 months, and that of Gonorrhoea as 4 days and if it is assumed that the average person in the United States received one injection of penicillin per year for a disease other than venereal, then the chance of receiving penicillin after infection and before diagnosis would be 1 in 6 in syphilis and 1 in 91 for Gonorrhoea and thus a coincidental 'happenstance' injection of penicillin is more likely to abort syphilis than Gonorrhoea. Side by side with a reduction in the overall attack rate of syphilis among the population after the advent of penicillin, there has been an increase in reinfections both symptomatic and asymptomatic. For thousands of years, the Treponeme has been living in a hostile unfriendly symbiosis with the human host, but now with penicillin therapy there appears to be a change in this relationship. The virulent invasive powers of the treponeme seems to have suffered a set back as witnessed in the low incidence of asymptomatic neuraxis involvement in untreated early syphilis. The French workers have brought forward some evidence from the study of syphilis in experimental animals, that penicillin may ultimately dethrone syphilis from its systemic status to one of purely local lymphatic involvement, provided the organism does not develope resistance to penicillin in the succeeding years. Whether penicillin will continue to be used as widely in the future as in the past, is in grave doubt, because of the increasing incidence of serious and often fatal sensitivity reactions and the development of resistance by a number of bacteria. But in the therapy of syphilis, penicillin still holds the field and the newer antibiotics both of the broad spectrum variety and the not-so-broad spectrum variety, have not established their equality with penicillin in therapeutic effectiveness.

The unitary concept is gaining ground that syphilis is only one facet of a widespread ancient disease-Treponematosis. Treponematosis may be regarded as a signal example in the realm of communicable diseases where the host-parasite relationship has changed with the changing environmental and socio-economic conditions of human population. The same disease is called Yaws when it is encountered among the harijan populations of Avanashi Taluq, endemic childhood syphilis or Bejel among the slum populations of urban Madras, venereal sporadic syphilis among the adults of either sex in the cities and seaports and pilgrim centres. The question may be posed "What does one know of Treponematosis who only knows Syphilis"?

In the current changing spectrum of disease patterns, it may be worthwhile both from an academic and philosophical points of view, to look back and see what has happened to a chronic disease when it was left to pursue its natural course. I have chosen Syphilis as an example of chronic disease for three reasons:

1. The most obvious reason is my familiarity with the disease during the greater part of my professional career.
2. Alone among chronic diseases of an infectious character syphilis is an example of exquisite chronicity extending from womb to tomb.
3. There is no where in the World's history any record either past or present of any large groups of population suffering from a chronic disease and remaining deliberately untreated. There is only one exception and that is syphilis.

Among chronic diseases of a communicable nature, Syphilis through the ages has always evoked interest and fascination among physicians, scientists. poets, dramatists and social historians unequalled by any other disease although in the current situation, the interest on the subject is 'at an all time low' in the expressive American phrasiology.

It has always been the case in the history of medicine, that when a cure has been found for a disease, the intellectual and scientific curiosity diminishes or vanishes, although there may be still unsolved problems connected with the disease. Syphilis is in that predicament now. Just at this psychological period a monumental and never - to - be - repeated epidemiological retrospective study of the natural course of untreated syphilis has appeared in a monograph of some 500 pages. The author of this study is one, Dr. Trygve Gjestland hailing from Oslo, Norway. Norway along with Sweden and Denmark were the pioneers in social and health legislation even as early as the last quarter of the 19th century. The public health laws of Norway required compulsory notification and hospitalisation of patients suffering from communicable diseases even at a period when the organismal cause of these diseases, was undiscovered. In Norway every patient hospitalised for early syphilis was required to sign a legal document which read as follows:

1. That I am suffering from Syphilis.
2. That my illness is infectious atleast for 4 or 5 years.
3. That it is under penalty of the law that I expose any other person to infection.

The administrative machinery was so highly organised in Norway that vital statistics, hospital records, health department records, marriage register, register of indigents, death certificates, autopsy records, population registers were all maintained in a highly efficient manner.

With this background information about the country, I wish to take the audience back sixty years in point of time and ask you to visualise an internationally reputed Professor of Dermato Venereology at the University of Oslo. He was Professor Caesar Boeck who practised a sort of therapeutic nihilism. He refused to treat syphilis with the only remedy then available that is Mercury in his ward, under the sincere conviction that Mercury far from curing syphilis generally interfered with the patient's own defence mechanism. From January 1891 to December 1910, approximately 2000 patients with Primary and Secondary Syphilis were admitted into Boeck's wards and hospitalised for varying periods without treatment until the clinical signs and symptoms had completely disappeared. The only concession to therapy which Boeck permitted was the administration of the non-specific Pot. Iodide in some cases. At that period of time, the diagnosis of syphilis was entirely based on clinical examination. No laboratory tests were available. Careful, reliable paintstaking records of all syphilis cases were maintained in a large central register. The cases were kept under day to day observation over period of months and the final diagnosis was entered only at the time of discharge from the hospital. Hence the margin of error of clinical diagnosis would be minimal.

It was left to Boeck's successor, E. Bruusgaard who was curious to know what happened to Boeck's patients after they left the hospital. In 1925–1927 Bruusgaard carried out an investigation and by means of personal examination and search of the hospital, clinic and autopsy records, he was able to get information on 309 living patients and 164 of those who had died. The total of 473 patients constituted 21·7% of the the original material at the time when the investigation was closed in 1927. In 1929 he published a paper giving his findings on the "fate of syphilitics who received no treatment". On a critical study of his findings it was found that his sample was highly selected and not representative of the original Boeck material or of untreated syphilis as a whole although his findings were quoted from text book to text book and in journals for about 2 decades.

Summary of Bruusgaard's data:
473 patients.

Patients showing at Examination or death:

Neuro syphilis	9·5%
Cardiovascular syphilis ..	12·8%
Benign late	12·2%
Latent syphilis	14·1%
Spontaneous cure ..	27·9%

Nothing happened till 1948, when a number of syphilis experts on either side of the Atlantic met and discussed the possibility of a restudy of the Boeck's material. Trygve Gjestland a junior colleague of Professor Danbolt the present holder of the chair at Oslo, undertook the restudy of the entire Boeck material, with the help and the co-operation of the United States Public Health Service, the Norwegian Public Health Service and three Universities of Oslo, Bergen and Columbia, not to mention a number of individual top ranking syphilologists.

Gjestland with a limited staff started the restudy in 1949 and completed the investigation in 1951. The careful planning, the tracing and identification of patients, the rechecking and cross checking of the identifying data and the laborious analysis of the enormous amount of information is a model of its kind and unexcelled in the field of medical research and is directly a tribute to the author and his staff, and indirectly to the country of his origin whose achievements in the field of social welfare and public health are well known. The aims of the author were to (1) trace as many patients as possible to an end point, defined as the last observation whether living or dead (2) to collect the maximum amount of clinical data on each patient from the date of his original discharge, all through the interim period of 40 to 60 years (3) to determine the cause of death through the available multiple sources of information and (4) to examine as many living patients as possible according to the most up-to-date clinical and laboratory investigations.

After a careful analysis of Boeck's records certain specific questions were formulated by Gjestland with a view to obtain answers from the collected data. The questions are:

1. What are the frequencies of (*a*) secondary clinical relapse (*b*) of benign tertiary syphilis (*c*) of late symptomatic syphilis (*d*) of life long latency (*e*) of spontaneous cure?
2. What are the effects on longevity, on causes of death and on mortality over that of non-syphilitics?
3. Does sex influence outcome?
4. What is the influence of age at time of infection on the ultimate outcome.
5. The effects on the outcome of pregnancy at varying intervals following infection.
6. Is a syphilitic more liable to suffer from other diseases than a non-syphilitic.

Gjestland confesses that the available data, cannot provide answers for each and every one of the questions formulated by him. A careful analysis of the reports of the syphilis registry of the department of Dermato Venereology at Oslo Hospital showed that 1978 patients with primary and secondary syphilis and secondary relapse had been discharged from Boeck's department during the 20 year period 1891–1910. Out of this number, the author took only 1404 patients excluding 574 non-Norwegians and non-residents of Oslo for the purpose of the study. The sex ratio of male to female was 1 : 2 and the mean age for the total group was 24·8 years with very little difference between the sexes. By stage of syphilis the vast majority were primary and secondary and secondary syphilis with a predominance of the purely secondary in females. In the study group there were about five per cent of children with acquired infection. The patients in the study mostly came from the under-privileged section of the population living in slum areas in Oslo. An analysis of the treatment status of the patients prior to, during and immediately after discharge from the hospital revealed that they were left untreated mostly except for the administration of Pot. Iodide in a percentage of the cases. The mean length of hospitalisation of the patient was 2·7 months for males and 3·9 months for females showing a marked difference. Among the study group investigated, 72 males (16·1%) and 187 females (19·5%) were alive at the time of the restudy in 1949–1951 while the dead about whom there was sufficient information were 259 males and 435 females (58·1% males and 49·4% females). Most of the living patients had passed the biblical limit of three score years and ten. On the question of treatment during the interim period of 40–60 years, Gjestland by laborious investigation and tracing the historical development of specific treatment available in his country during the successive decades of the long interim period, concludes in about 83·4% of patient, there was no treatment. The results of the final analysis of the collected data are presented and discussed in separate chapter headings. At the sametime he has reviewed the pertinent literature on the subject.

1. Clinical Secondary Relapse:

Most of the modern Syphilogists have stated that clinical secondary relapse occurs only in inadequately treated Syphilis and never occurs in untreated syphilis. Gjestland has debunked this concept, by his study of the Oslo material and found about 25% of the patients had relapsed one or more times, during a period of 2 years after discharge from hospital. The sites of relapse were-muco cutaneous in 84·8%; ocular in 6·1%; and skeletal in 2·2%. An interesting and significant feature in the study of secondary relapse is the almost complete rarity of Neuro recurrence. In order to test the commonly held hypothesis that patients with clinical secondary relapse are more prone to develop serious late manifestations, the author of the study analysed his cases and found that there was no statistically significant difference in the development of late lesions between relapsers and non-relapsers.

2. Benign Tertiary Syphilis :

15·8 percent developed benign late syphilis and a third of this number experienced more than one outbreak of benign tertiary syphilis. A break down by sex revealed that benign tertiary syphilis seemed to occur earlier and was more frequent among females in contrast to what appears to be the case in cardiovascular syphilis and neurosyphilis. The mean duration of infection was 11·6 years. The sites of involvement were:

(*a*) skin in 70%
(*b*) Skeletal in 9·6%
(*c*) mucous membrane in 10·3%

12.1% experienced precocious tertiary lesions within the first two years after infection.

Gjestland tested the validity of the commonly held belief in the protective and preventive effect of benign tertiary syphilis against the development of serious cardiovascular syphilis and neurosyphilis, by using three indices when analysing the Boeck material:

1. The frequency of the concomitant incidence of Benign tertiary with cardiovascular syphilis and neurosyphilis.
2. How many cases of cardiovascular syphilis and neurosyphilis were preceded by the occurrence of Benign tertiary syphilis.
3. Frequencies of serious late manifestations in those who had experienced Benign late syphilis and those who had not suffered from Benign late syphilis - by a follow-up study.

By the first index, only 2 out of 92 cases of cardiovascular syphilis and 5 out of 62 cases of neuro syphilis were observed to have developed Benign tertiary lesions simultaneously, thus appearing to lend support to the currently held concept. But on the basis of the widely differing incubation periods of the three types of syphilis - 11·6; 21·1; 32·9 years, the rarity of concomitant lesions is understandable. When tested by the 2nd index it is found that the proportions of benign tertiary syphilis that preceded the serious late manifestations were not smaller than the proportions in the study group as a whole, indicating the absence of any protective effect.

18·4% cardio vascular - preceded by B. T. S.
16·1% Neuro syphilis ,, ,, ,,
16·3% of Benign tertiary in the study group as a whole.

When analysed by the third index, far from indicating any evidence of a more favourable outcome among those who were known to have had Benign tertiary syphilis, the study shows on the other hand, consistently higher incidence of C. V. S. and C. N. S. among them. Hence by all the three indices, Gjestland proved that B. T. S. does not seem to protect against C. V. S. and C. N. S.

To sum up, the author of this study has made a significant contribution to the study of syphilis in disproving the currently held views on (1) Pathogenesis of secondary clinical relapse, (2) Prognostic gravity of clinical secondary relapse in respect to the latter development of serious late lesions and (3) on the protective effect of Benign tertiary syphilis against serious late syphilis. He has further in the writer's opinion performed a distinct service to tropical syphilology about which there is a lot of loose thinking and unverified assumptions. It is oft said and repeated that the paucity of serious late manifestations of syphilis of the cardiovascular and central nervous systems in tropical and near tropical countries of the world is due to the protection afforded to these tissues by antecedent florid and destructive lesions of the skin and skeletal systems both early and late.

3. Neuro-Syphilis:

In the study group, the incidence of neuro syphilis was 6·5% (males 9·4 and females 5·0) ratio male to female : 2 : 1. In this group of 62 patients, there were four cases of neuro syphilis in patients who acquired syphilis in childhood under 15 years of age.

Types of neuro syphilis—diffuse meningo vascular, General paresis, Tabes dorsalis, and gumma of the brain in descending order of frequency, are the form. Among the paretics (20 in the series) there was one interesting case recorded of a patient infected in 1896 at the age of two. General Paresis was diagnosed in 1931 when the patient was 37 years old. He was successfully treated with Malaria. He was alive and well in 1951 at the age of 57 years. The mean duration of infection varied in the three major types–meningo vascular 18·8 years, General paresis 19·7 years and Tabes 36·8 years. Neuro syphilis was the primary cause of death in 63·6% of the dead known to have suffered from Neuro syphilis. The author in discussing the influence of treatment in the incidence of neuro syphilis quotes with approval the following statement by Moore 'Treatment adequate or inadequate appears to have no influence in increasing the incidence of any form of clinical neurosyphilis except acute syphilitic meningitis.'

4. Cardiovascular Syphilis:

Gjestland in his study has excelled himself in his presentation of the subject of cardiovascular syphilis which is the Waterloo not only of the physicians but also of the host in his fight against the insidious treponemal invader. The reader is referred to the chapter in the monograph for a proper understanding and further appreciation of the subject of cardio-vascular syphilis. The author has at great length reviewed the pertinent literature on the subject of cardiovascular syphilis with reference to diagnosis, sex, age, duration of infection, occurrence, occupation and prognosis and after presenting his own data has discussed the many controversial as well as the generally accepted features of this most fatal of all complications. For the purpose of the study cardiovascular syphilis was classified into two broad categories - uncomplicated aortitis and complicated aortitis, the latter subdivided into aortic regurgitation, aortic aneurysm and osteal stenosis. He discusses the controversy over the clinical diagnosis of uncomplicated aortitis. The gross discrepancy between the clinical and autopsy evidence of uncomplicated aortitis reported in the literature and in his study of the Boeck meterial goes to prove, that only in a limited number of cases has clinical diagnosis been proved correct by subsequent confirmation by autopsy. From the study of the pertinent literature, Gjestland states that there is definite evidence that adequate treatment given for early syphilis appears to prevent the subsequent onset of cardiovascular syphilis in almost 100% of cases. In the study group there were 92 cases of cardiovascular syphilis constituting 10·4 percent of the untreated group. The diagnosis was verified by autopsy in 60% of the cases. 22 of the 25 cases of uncomplicated aortitis was only discovered at autopsy. There were no cases of cardiovascular syphilis among the 62 patients who acquired syphilis in childhood, Thus it would appear that in respect to the development of cardiovascular syphilis, congenital infection as well as infection acquired in childhood run a milder course than would be expected. The total of 10·4% of the patients with cardiovascular syphilis in one form or other consisted of 2·8% of uncomplicated aortitis and 7·6% of complicated aortitis. On a sex specific basis, the predominance of occurrence in the males over that in the females is observed with a ratio of 1·9 to 1. The excess of sex difference is seen in all the complicated forms and in the total as well. There was no significant difference between the sexes in the occurrence of uncomplicated aortitis. The factors of hormonal influence in pregnancy and menstruation, occupational stress and physical activity in the causation and frequency of cardiovascular syphilis are discussed by the author in some detail and the study seems to suggest that occupational stress and physical activity may explain the extent to which these complications are going to develop and may also account for the difference in incidence between the sexes.

The duration of infection at the time of recognition of cardiovascular syphilis irrespective of the type was 31·4 years in males and 31·7 years in females. Cardiovascular syphilis was the primary cause of death in 61% of the male cases and in 47·6% of the female cases. On going through the two chapters on neurosyphilis and cardiovascular syphilis, the speaker noted there is no reference to the collateral presence of neurosyphilis and cardiovascular syphilis in the study material, Since the average duration of syphilis in Boeck's patients at the time of the Investigation was 50 years and since the incubation periods of the two late complications are different, one would expect a certain proportion of patients showing clinical evidence of both the complications. It is possible that the study material did not furnish information on this question.

Mortality :

There is general agreement among experts about the fact of the excess mortality among syphilitics untreated or inadequately treated. Two theories are advanced to explain the phenomenon :

1. Syphilis is predominantly a disease of the underprivileged sections of society. These sections besides being exposed to the health hazards of syphilis *per se* are naturally exposed to the risk of a host of other diseases more commonly encountered in such population groups. Hence they would be expected to show a greater mortality from all causes than non-syphilitics do. Hence it is logical to infer that syphilis can only be partly held responsible for the excess mortality.

2. Syphilis as a generalised systemic disease, besides causing death primarily as a result of the infection may exert a deleterious non-specific effect on most of the organ systems of the body, thereby increasing the morbidity and mortality from a large number of illnesses other than syphilis. In the Oslo study material, Syphilis was the primary cause of death only in 15·1% of males and 8·3% of females. In a 100% syphilitic population, 84·9% of males and 91·7% of females died of other causes. How far in the latter group was syphilis a secondary cause of death could not be known. By a comparison of the mortality experience of two control groups the lower and the higher socio-economic sections in the city of Oslo, Gjestland is inclined to the view that the excess mortality found among the syphilitics can be explained on the basis of the

fact that they come from the lower socio-economic strata of the population who in addition to syphilis were victims of other diseases. Syphilis kills only through the lethal effects of its serious late manifestations.

Spontaneous Cure :

The stringent criteria laid down by Moore for defining spontaneous cure are as follows: " In a group of originally untreated syphilitics, a diagnosis of spontaneous cure should fulfil the following conditions. The patients, (1) had shown no symptoms of syphilis after the early outbreak, (2) had received no specific treatment for latent syphilis during the interim period, (3) had been examined before death with normal physical findings as far as syphilis was concerned, and who then had a negative serological test and normal spinal fluid, (4) had at autopsy shown no evidence of syphilis. The author states there has been no representative group of patients including the Oslo group who could satisfy these rigid almost impossible criteria. But from the point of view of individual patients, Gjestland from the study of the voluminous data he had collected, found a large number of the untreated or inadequately treated syphilitic patients had passed through life with little or no inconvenience as a result of the disease. From the study material, it would appear only 28% were found to have developed some type of late manifestations, while 72 out of 100 patients were found not to have developed any late lesions. After recognising the fact that his figures on the various complications represent a minimum, Gjestland concludes by saying that somewhere between 60 and 70 (probably closer to 60 than to 70) out of every 100 untreated syphilitics in his series went through life with little or no inconvenience as a result of the disease.

The speaker has attempted to give a short resume of the natural course of a chronic disease (Syphilis) from the monumental study of Boeck's syphilis material by Trygve Gjestland, and would recommend that the monograph in original should be read by all physicians. From the prognostic point of view, the study reveals that the human organism is capable of vanquishing the treponemal invader by its own unaided defence mechanism in a large number of cases. But it does not follow that a Laissez-faire attitude is justified. Both on public health principles and from the impossibility of foretelling in any individual case of untreated syphilis whether he is likely to develop serious late complications, it is incumbent that syphilis as a communicable and social disease should receive adequate treatment particularly when specific drugs are available.

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"PEMPHIGUS"

by

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PEMPHIGUS is an essentially bullous skin lesion. Great advance in knowledge is aided by histopathological studies of the lesion. The varities of Pemphigus are :—

1. Pemphigus acutus.
2. Pemphigus vulagris.
3. Pemphigus foliaceus.
4. Pemphigus vegetans.
5. Pemphigus erythematoides,
6. Familial benign chronic Pemphigus of Hailey and Hailey.

1. Pemphigus acute :—The onset is sudden and there are severe constitutional disturbances. The lesions occur in the mouth or about the neck, trunk and other parts of the body. The eruptions are bullae and vary in size. The bullae are oval and contain fluid which is sterile at first but later becomes purulent or haemorrhagic. Most of the patients have had contact with dead animals, being butchers or trappers aetiology, (1) Occupational contact with dead animals. (2) The disease is propably in the nature of Schwartzman phenomenon.
Histopathology of skin. (Vide diagram 1.)

The bullae are found between stratum corneum and rete malphigi. The bullae contains a fibrous network with rete cells.

Treatment :—The administration of A. C. T. H. or Cortisone is beneficial.

2. Pemphigus vulgaris :—The lesions contain bullae of various types. The condition is insidious onset. The lesions are found in various parts of body. The mucous membrane the face and neck are less commonly involved. The bullae characteristically arise on the normal skin, but a zone of erythema may surround the bulla. The bullous lesions contain a clear serum. The lesions rupture and crust formation takes place.

Nikolosky's sign :—If the thumb is pressed on apparently normal skin in a case of pemphigus the superficial part of the skin becomes denuded.

Histopathology of skin in Pemphigus vulgaris :—Vide diagram 2 and 3.

The features are :—1. Intraepidermal suprabasal bulla.

2. The bulla contains many acantholytic cells. (Acantholysis is loss of coherence between epidermal cells due to disappearance of intercellular bridges.)

These cells show degenerative changes : They are round and swollen and show hyperchromatism surrounded by a narrow zone of homogenous cytoplasm. These are known as Tzanck cells. These cells may be obtained for diagnoestic purpose by (*a*) scraping from floor of the bullae (*b*) smears from bullous fluid, (*c*) biopsy smears from bullae, (*d*) paraffin fixed sections of lesions.

3. Pemphigus Foliaceus :—This is a rare type of pemphigus where the following features are present. A flacid bulla appears and ruptures readily and discharged the contents and leaving an excoriated reddish or purpulish surface. The contents of the bullae are at first pellucide and later become purulent or sanguinolent. Then the blubs rupture ; yellowish brown crusts form in the centre and edges remain free. The edges show polycyclic outlines. The disease affects the mouth, the throat, and affects the body symmetrically. The scalp also may be involved. There may be fever in the later stage disease.

Histopathology in Pemphigus Foliaceus: Vide diagram 4.

The changes are acantholysis of the upper epidermis usually in the granular layer. Bullae may not be seen. In the dermis a moderate number of inflammatory cells chiefly eosinophils may be seen.

4. Pemphigus Vegetans :—The initial lesions are bullous but these soon rupture and vegetative plaques appear. The disease is marked by languor and malaisa, febrile symptoms of moderate severity and impairment of health. The lesions may occur in the mucus membrane of the mouth of genitalia but are more common on the trunk.

Histopathology of Pemphigus Vegetans:–

Vide diagram 5.

The following are the characteristic features. Acantholysis and bullae formation are similar to other types of pemphigus. But the chief factor is the occurrence of intra epidermal abscesses composed almost entirely eosinophils.

5. Pemphigus erythematosus :—This is called Senear-Usher syndrome. This is a comparitively a benign type of chronic pemphigus. The lesions resemble lupus erythematosus and seborrhoeic dermatitis but bullae which form the diagnostic feature pemphigus is an important sign and should be looked for. Histopathology in pemphigus erythematosus :—The histological picture resembles pemphigus foliaceus. The other features present in the disease are, (*a*) Follicular hyper keratosis and by dyskeratosis (Faulty keratanization) of the granular cells. The histopathological picture of lupus erythematosus shows hydropic degeneration of basal cells and patchy inflammatory infiltrate in the dermis. These are absent in Senear-Usher syndrome. The chronic pemphigus of Hailey and Hailey may be discussed later as it belongs to a separate group.

In the meantime the discussion may be centered over the etiology of the varities of chronic pemphigus, described supra. Dr. Lever is frank in stating that till now the search for the cause of pemphigus has been fruitless as the search for philospher's stone. Still the zeal and enthusiasm for the cause continues. The retention of the salt as cause of pemphigus has been subject to many investigations and still nebulous. The positive pels & Macht test postulating a toxic origin has not found favour.

Dr. Waelsch, Radaeli & Eberson believe in a bacterial origin for pemphigus. They isolated streptococci in cultures from the fluid in the bullous lesions. Dr. Urbach urges a viral origin and Dr. Grace found neutralising antibodies.

Dr. Stoaghton's experiments with various proteolytic enzymes in vitro on human skin leads to a possibility in producing pemphigus.

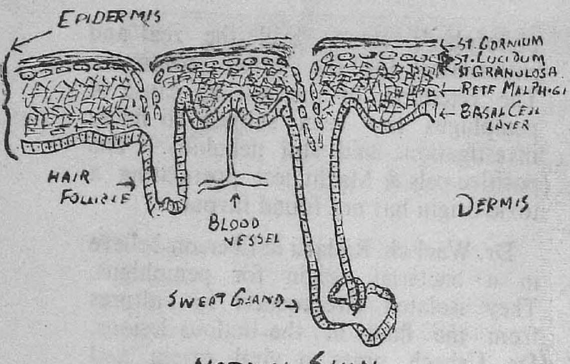
The treatment of pemphigus :- 1. The patients with pemphigus should be hospitalised and put on a high protein diet. 2. It is advisible to treat any co-existing anaemia by blood transfusion. 3. Local therapy : The local measures are cleansing, with 1 in 25,000 pottasium permanganate and apply externally Hydrocortisone as Efcorlin (Glaxo) skin lotion. I have found this method to be good in my cases. 4. The systemic administration of A. C. T. H. or cortisone produces marked remission.

6. Familial benign chronic pemphigus Hailey & Hailey :—This condition occurs as vesicular & bullous lesions distinctly familial in origin. The lesions occur on the sides of neck, axillae and other flexures. These rupture become covered with crusts. There is no etiological factor except familial and hereditary nature.

Histopathology skin :— The histopathological features are :—

1. Definite acantholysis is present.
2. Tzanck cells are not found.
3. Dyskerotosis also occurs.
4. The lesions in this type have intact roofs even in the bullous forms.

Treatment :— This is similar to other bullous dermatosis.



NORMAL SKIN.

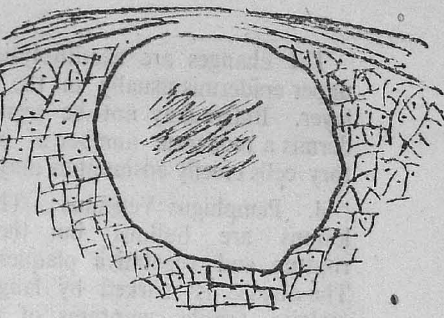


FIG 2

P. ACUTA.

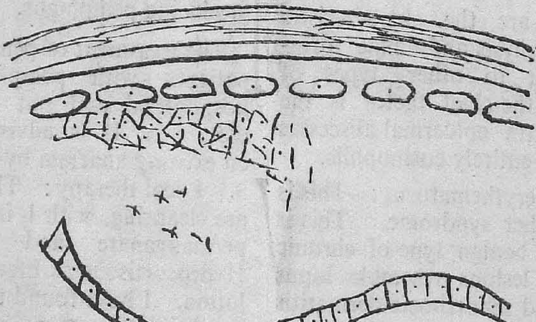


FIG. 3

P. VULGARIS.

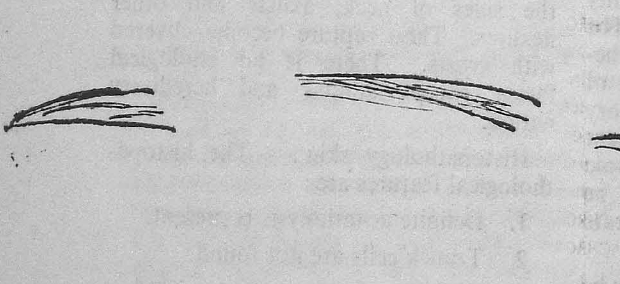


FIG 4.

P. FOLLIACEUS.

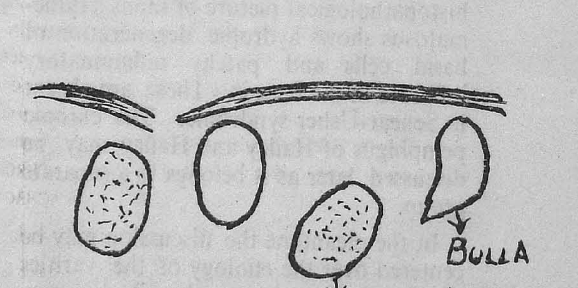


FIG. 5.

P. VEGETANS.

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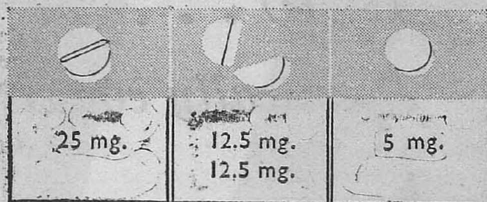

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Efcorlin Eye Ointment,
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* NON-TUBERCULOUS BACTERIAL INFECTIONS OF THE KIDNEY.

by

Dr. H. A. SATYA JOSEPH, M. B., B. S.; M. R. C. P.; D. T. M. & H.;
Madurai.

How may these infections occur?

1. **Primary**: involvement of the urinary tract by organisms which are non-pathogenic in their normal habitat like the upper respiratory or intestinal tract.

2. **Secondary**: to a recognisable focus of infection elsewhere in the body, *e. g.* an abscess, boil, Osteomyelitis etc.

Modes of infection:

1. **Haematogenous spread**: following bacteraemia from a focus in the body, *e. g.* boils and furuncles, whitlow or some suppurative lesion of bone or joint. Nidi of infection occur in the kidney and the thus damaged kidney excretes the bacilli into the pelvis infecting the latter as well.

2. **Lymphatic spread**: (*a*) By lymphatics from the intestinal tract, particularly the large intestines to the medulla of the kidney and pelvis.

(*b*) By periureteral lymphatics from the lower urinary tract to the pelvis and kidney.

3. **Combined spread**: The infection first spreads from the lower urinary tract and intestinal tract to the abdominal lymph glands; from the lymph glands it gets into the blood stream through the thoracic duct; and then haematogenous spread occurs.

4. **Direct ascending infection** by way of the ureter from the lower urinary tract. For this to happen there should be obstruction, stasis and infection in the lower urinary tract.

Common Causes of obstruction and stasis:

In the female (1) Pregnancy causes dilatation of the pelvis of the kidney due to hormonal imbalance causing atony of the ureters.

(2) Prolapse of uterus and cystocele.

(3) Carcinoma of pelvic organs.

In the male (1) Enlarged prostate.

(2) Stricture urethra.

In both sexes (1) Calculi.

(2) Nervous causes giving rise to the "cord" bladder.

"Cord" bladder may be sensory as in Tables dorsalis or motor, where there is paralysis of the bladder musculature as in paraplegia, transverse myelitis, traumatic myelitis, gross spina bifida etc.

Bacteriology of infections of the kidney: More than 75% of the infections are due to Esch coli. Next in frequency are the Staphylococci and streptococci. More rarely the infection is caused by *Proteus vulgaris* and *Pseudomonas pyocyaneus*; and still more rarely it is caused by gonococci.

Usually pyogenic cocci are responsible for infections of the cortex, while the colon bacillus is responsible for infections

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* Based on part of a lecture delivered at the monthly meeting of the Madurai Branch of I. M. A. on 22-12-56.

of those portions of the kidney nearer the pelvis and the pelvis itself.

Acute infections (Acute pyelonephritis).

Esch coli infections: It is said that a preceding infection of the intestines, *e. g.* appendicitis or diverticulitis, is the source for this type of infection. But it should be remembered that many people suffer from such complaints for years without any renal infection, and many cases of renal infection have no such bowel disorders.

From the intestines the infection spreads to the kidney by means of lymphatics. Small coliform abscesses are formed in the interstitial tissue of the medulla, from where the abscesses rupture into the pelvis and also extend into the cortex. Thus, these renal infections are always a pyelonephritis, the infection of the kidney substance preceding the infection of the pelvis. In the case of ascending infection from the lower urinary tract, the pelvis is affected first and then the kidney substance nearest to the pelvis, this again constituting a pyelonephritis. To prevent recurrence therefore, the infection in the kidney substance must be cleared up completely; otherwise chronic pyelonephritis will be the end result, and chronic pyelonephritis is a very important cause of renal failure.

Clinical features: The onset is usually sudden, with rigor, rapid rise of temperature to 100° - 103° F and headache; there may be vomiting; there is pain over one or both kidney regions radiating along the course of the ureter down to the suprapubic area and sometimes even down to the genitals; there may be tenderness over one or both kidney regions; there is often dysuria and strangury with the frequent passage of small quantities of cloudy urine; there is usually a leucocytosis.

In children, pyelonephritis may occur without prominent urinary symptoms and may present only the general features of fever, possibly initiated by a convulsion. Under such circumstances the urine must always be examined microscopically.

The urine in Esch coli infections becomes acid (pH 5·5 or less) even before pus occurs in the urine. Pus and motile organisms appear in the urine later, when the coliform abscesses rupture into the pelvis of the kidney.

B. proteus infections. The source for such infections is the intestines. The infection spreads in the same way as in the case of **Esch coli** infections and causes pyelonephritis.

The urine in **B. proteus** infections is highly alkaline (pH 8 or more) and contains pus cells and motile organisms.

Gonococcal infection is usually a direct ascending infection; there may not be any renal involvement at all; but at times the infection spreads to the kidney tissue also.

The urine in gonococcal infections is acidic; stained deposits show pus cells and the characteristic diplococci.

Staphylococcal infections. Usually the source is a boil, furuncle or Osteomyelitis. The infection is always bloodborne to the kidney substance. The lesions can be of three varieties :—

(*a*) Multiple lesions occur in the cortex of the kidney; these form abscesses and the condition is one of diffuse suppurative nephritis.

(*b*) These pyaemic abscesses may form in the sub-capsular region.

(*c*) A single large abscess may form in the cortex constituting a renal carbuncle.

The urine in staphylococcal infections is just on the alkaline side, the pH being 7–7·5, so that it is easy to acidify the urine unlike the urine in the case of *B. proteus* infections. There may be only a few pus cells in the urine.

Clinical features are usually the same as in the case of *Esch coli* infections, but the temperature may be higher, the leucocytosis may be more, and the pain and other constitutional symptoms may be more severe.

Renal carbuncle. The constitutional symptoms are very severe and toxaemia is marked. A tender kidney tumour can often be felt. The carbuncle ultimately bursts into the perinephric tissue or the pelvis of the kidney. When the latter occurs, a large amount of pus appears suddenly in the alkaline urine with the disappearance of the kidney tumour and the general toxaemic symptoms.

Perinephric abscess is formed by :—

(*a*) Rupture of a renal carbuncle into the perinephric tissue.

(*b*) Rupture of a sub-capsuler abscess.

(*c*) Sometimes perinephric abscess has been known to occur without any associated kidney lesion.

Some of the clinical features are, the severe constitutional symptoms, leucocytosis, pain, tenderness and swelling in the costovertebral angle, and spasm of the psoas muscle.

Streptococcal infections: Three varieties can occur and these are caused by pyogenic, non-pyogenic and intestinal streptococci.

Infections due to pyogenic streptococci: The source of infection is the mouth or upper respiratory passages or ulcerative endocarditis and the mode of infection is haematogenous. Diffuse suppurative nephritis occurs as in the case of staphylococcal infections.

Infections due to non-pyogenic streptococci or Str viridans: The source of infection is often a subacute bacterial endocarditis and the spread is haematogenous. Embolic nephritis occurs due to impaction of the organisms in the glomeruli. But no pyuria occurs because the organisms are non-pyogenic. Only microscopic haematuria occurs.

Infections due to intestinal streptococci or Str faecalis: The source of infection is the intestines and the mode of spread is either lymphatic or ultimately haematogenous via the abdominal lymph glands and thoracic duct.

Chronic infections (chronic pyelonephritis).

Aetiology. (1) The disease may follow an inadequately treated acute attack.

(2) It may also be caused by infection above an obstruction, e. g. Calculi, Stricture, enlarged prostate.

3. Other cases may be due to stasis as in cystocele, tabes and paraplegia.

Bacteriology: **Esch coli** is the organism responsible for the vast majority of these chronic infections.

Clinical features: The three cardinal features are, dull aching lumbar pain, moderate increase in frequency of micturition more noticeable at night, and slight pyuria.

In all cases of chronic pyuria therefore, even in the absence of symptoms, investigations such as rectal or vaginal examinations, cystography and pyelography must be carried out to determine the site of infection and the nature of any underlying mechanical factor causing obstruction to the flow of urine. Chronic unilateral pyelonephritis can be distinguished from bilateral involvement only by urologic studies.

Course of acute pyelonephritis: It is cured completely or becomes chronic with acute exacerbations from time to time.

Course of chronic pyelonephritis: is one which extends over many years with acute exacerbations. In long-standing cases there is atrophy of the tubular epithelium and fibrosis of the tubules giving rise to tubular failure, without however any urea retention or rise in blood pressure. As the disease progresses renal glomerular function also becomes impaired with urea retention and rise in blood pressure giving rise to a picture similar to that which occurs in Chronic glomerulonephritis.

Management of urinary infections: Three points should be borne in mind in treating urinary infections and they are :-

1. The condition is one of pyelonephritis and not merely of pyelitis. Hence there is no point in using only urinary antiseptics. Tissue penetrating agents must also be used.

2. Treat for complete cure and not merely for alleviation of symptoms; otherwise the condition may go on to the chronic stage.

3. Remember the importance of obstruction and stasis in perpetuating the infection. During treatment there must be adequate drainage from the pelvis. Hence, full investigation in collaboration with a surgical urologist if need be, is necessary to rule out obstruction.

Treatment of acute pyelonephritis:

1. Arrive at a complete diagnosis as regards the condition and the cause of the condition as early as possible.

2. Bring the patient under treatment early.

3. Identify the causative organism by cultural reactions and test its sensitivity to the various antibiotics. For culture, catheterised specimens from females and midstream specimens from males should be used.

Treatment: is symptomatic and specific.

Symptomatic treatment consists of :—

1. Rest in bed.

2. Warmth to the loins to relieve the pain.

3. Giving plenty of fluid by mouth, upto 3–4 litres per day.

4. Reversal of the reaction of the urine.

In *Esch coli* infections where the urine is highly acid, it should be made alkaline by giving 150–250 grains of alkalies per day. But the urine should not be made overalkaline for fear of producing phosphaturia, which in the presence of stasis is likely to perpetuate the infection.

The alkaline urine of *B. proteus* infections should be made acid by giving large doses of ammonium chloride.

Specific treatment: Usually one can wait for the sensitivity reports before instituting specific treatment. But if one cannot afford to wait, begin treatment with Sulphonamides alone.

The sulphonamide used must have the following characteristics :—

1. **Low acetylation**: Sulphonamide is excreted in the free form and as acetyl sulphonamide after acetylation. Sulphonamide becomes inactive after acetylation and therefore unless the sulphonamide used is one with low acetylation, effective concentrations of active sulphonamide will not be reached in the contents of the pelvis of the kidney.

2. **High solubility**: The more soluble the sulphonamide, the less is the chance of renal damage. It may be assumed

that the danger of renal damage ceases when the solubility exceeds 100 mgns %.

3. **Must be capable** of attaining effective concentration in the blood and thus capable of tissue penetration in effective concentration. Unless this is achieved there is a chance of the infection in the kidney substance becoming chronic.

Considering all these, Sulphamezathine or Sulphadimidine is one of the best sulphonamides to use. Elkosin (Ciba) has a high solubility, low acetylation (10%), has good tissue penetration because it is present in the blood in effective concentration and it is also capable o attaining effective concentration in the urine. Urolucosil and Gantrisin are also good sulphonamides to use.

Whatever sulphonamide is used, the dosage should be ample and it should be administered for a sufficiently long period-say two weeks. Plenty of fluids and alkalies should be administered along with the sulphonamides. After two week's treatment, stop the drug for two or three days, and culture the urine again. If there is persistence of infection, sensitivity tests should be done again and treatment reinstituted with another course of sulphonamides or with appropriate antibiotics.

Treatment with antibiotics depends upon the sensitivity of the organism to the various antibiotics. As a rough guide :—

Esch coli responds to Streptomycin, Chloramphenicol and Aureomycin.

B. proteus responds to Chloramphenicol and Streptomycin.

B. pyocyaneus responds to Streptomycin and Chloramphenicol.

Str faecalis may be resistant to individual antibiotics, but may be sensitive to a combination of Penicillin and Streptomycin.

As in the case of sulphonamides, the antibiotics should be given for a sufficiently long period in adequate dosage. The antibiotic is then discontinued for a couple of days and the urine cultured again to determine whether the infection has cleared up or not.

I would like to mention a few words about the use of Streptomycin in the treatment of renal and urinary infections. By correlation of in vivo and in vitro sensitivity of organisms, it has been found that small doses of Streptomycin given over a longer period are as effective as large doses given for two or three days. Thus it has been found that 0·25 to 0·5 G. twice a day for seven to fourteen days is as effective as 2–3 G per day for two or three days. The advantages of the "Small dose-long period" schedule over the "Large dose-short period" schedule are that the chances of producing resistant strains are less and that Streptomycin can be used with advantage in case of recurrence. It is also worth remembering that alkalies should be given freely during the period when Streptomycin is administered.

Facilities for culture may not be available everywhere and at all times. But a clue as to the identity of the causative organism can be obtained by testing the p^H of the urine by means of the B D H universal indicator and by microscopic examination of the deposits. *E. g.* If the urine is highly acid and motile organisms are seen in the deposit, the infecting organism is likely to be *Esch coli.*

If the urine is highly alkaline and motile organisms are seen in the deposit, the infecting organism is likely to be *B. proteus.*

The choice of the chemotherapeutic agent in such cases has to be necessarily empirical and if there is not adequate response to a particular course of treatment, a change over to another chemotherapeutic agent is made, again empirically.

Occasionally there may be a few cases which do not clear up completely with the above treatment. In such cases Mandelic acid or Hexamine mandelate (Methenamine) may be tried. Mandelic acid must be administered in adequate dosage (say 50 gr. four times a day) to obtain high urinary concentration (0·5 mgm. %). The urine must be maintained sufficiently acid, with ammonium chloride if necessary, so that the pH is less than 5·5. At this acidity the urine gives a pink colour with methyl red indicator.

Hexamine Mandelate is supplied as tablets of 0·25 G. each.

Dosage: 3–4 tablets, three or four times a day.

Proof of cure: Absence of pyuria alone is not the criterion of cure. Two catheterised specimens of urine taken at an interval of four days should be sterile on culture.

Treatment of chronic pyelonephritis: Consists primarily of prevention, treatment of acute exacerbations and removal of obstruction and calculi. Prevention is achieved by timely, efficient and adequate treatment of acute pyelonephritis.

The treatment of acute exacerbations is on the lines as outlined for the treatment of acute pyelonephritis and therapy should be continued until microscopical and bacteriological examinations of the urine are persistently negative.

Obstruction must be relieved and calculi removed by appropriate surgical measures.

If urologic study shows that the pyelonephritis is unilateral and the function of the other kidney is good, surgical removal of the affected kidney should be considered.

Treatment of renal carbuncle and perinephric abscess is surgical drainage combined with the administration of suitable antibiotics.

ASSOCIATION NEWS

COIMBATORE BRANCH

A meeting of the Association, was held on Sunday the 7th July 1957 in the Association premises. Dr. Y. P. Vasudevan, M.B.,B.S., B.S.SC., presided in the absence of Dr. T.V. Sivanandam, M.B.,B.S., M.L.C., President of the Association.

Dr. I. G. K. Menon gave an analytical review of the recent epidemic of Influenza and postmortem findings of the fatal cases and also stressed the value of iodine in the treatment of influenza.

ERODE BRANCH

A meeting of the Association was held in the residence of Dr. C. R. Tiruvengadam, M.B.,B.S., Erode. Dr. T. S. Bhaskaran, M.B.,B.S, presided. At the outset the President said that he had nominated Dr. L. K. Muthuswamy as Hony. Secretary till the return of Dr. M. N. Shenoy. Dr. C. R. Tiruvengadam took the doctors around the hospital and demonstrated some interesting cases.

MADRAS CITY BRANCH

A Special General Body Meeting of the Association was held on Thursday the 8th August 1957 at the Madras Medical College to elect President and three Vice-Presidents to the Parent Body for the year 1957–58.

MADURA BRANCH

The monthly meeting of the Association was held under the Presidentship of Dr. K. Balakrishnan, M.B.B.S., T.D.D., on the 20th July '57. Dr. R. S. Padaki, M.B.,B.S. F.R.C.P.S., D.M.R.E., spoke on the "Eastern Psychology."

*   *   *

The monthly meeting of the Association was held on Thursday the 15th August '57 in the Association Building, Madurai. Dr. A. Venugopal, M.S., F.A.C.S., (Honorary Surgeon, Government General Hospital, Madras), delivered a lecture on "Cancer of the Bladder". Election of Vice-Presidents for Madras State Branch of I. M. A. was also held. A film show on "Migraine" and "Epilepsy" by the courtesy of Messrs. Sandoz Products Private Ltd., Bombay was shown after the lecture.

NILGIRI BRANCH

The monthly meeting of the Association was held on 27th July 1957 at Pasteur Institute, Coonoor.

Dr. A. Balasubramanian, M. B., B. S., Medical Officer. Pasteur Institute, Coonoor, addressed on "Intestinal Viruses".

Election of one President and 3 Vice-Presidents to Central Committee of I. M. A. was held.

TIRUCHI BRANCH

A Monthly meeting of the Association was held on Saturday the 27th July, 1957 in the premises of the Medical Association Buildings, Salai Road, Woriur, Tiruchi. Dr. K. G. Menon presided.

Dr. B. S. Viswanathan, L.M.S., T.D.D., Superintendent. Ramalingam Tuberculosis Sanatorium, Perundurai, addressed the members on "The Management of Tuberculosis".

Election of one President and Three Vice-Presidents for the Central Office for the year 57–58 was held.

The Fifth Madras State Ophthalmic Conference - 1957.

COURTALLAM.

NOTICE

The above Conference will be held on the 14th and 15th September 1957 at Courtallam, a salubrious place with good water falls in Tirunelveli District of our State.

Dr. P. Sivasubramaniam, L.M.S. (Ceylon), D.O.M.S. (London), F.R.C.S. (England), Visiting Surgeon, Victoria Memorial Eye Hospital, Colombo has kindly consented to preside over the Conference, and Hon. Dr. U. Krishna Rao, M. B., B. S., Speaker, of the Madras Legislative Assembly has agreed to declare the Conference open at 2 P. M. on 14—9—1957.

All the delegates will be accommodated in the Dalavoi House, a hotel with good Boarding and Lodging, free of cost.

Families. Rs. 9/- per head per day will be charged for the duration of the Conference, at the cost of the delegates bringing their families. Those who wish to come a few days earlier, may write to the Manager, Dalavoi House, Courtallam and make their own arrangements.

As for the *Servants* of the delegates, they are requested to make their own arrangements.

Those attending the Conference are requested to intimate the convener positively before 7—9—1957, with details of the number of members of their families accompanying, to facilitate arranging accommodation etc.

Intimation of arrival. Should be done early enough to the convener as to: (1) the time at which they will arrive at Tenkasi or Shencottah railway station by train, or (2) the probable arrival time at Courtallam by any other conveyance, & (3) the number of members arriving. A special conveyance will be waiting for those giving previous intimation.

Reservation of seats for return journey by train. Will be done for those sending the correct required amount *by money order* clear seven days before the Conference with details.

Information. *Railway*: Nearest Railway station - Tenkasi from Madras side & Shencottah from Trivandrum side. *Postal:* Dalavoi House. *Telegrams:* 'Castle' *Telephone:* Extn. No. 7.

Panel discussion. It is proposed to allot an hour for the discussion of individual problems and difficulties of the practitioners. If these are sent to the Convener in the form of questions atleast three days before the Conference, these will be sorted and the most important will be placed before the meeting for answer by eminent Opthalmologists attending the Conference.

Convener's Address :—

DR. N. C. SEKHAR, M.B.B.S., D.O.,
Narayan Eye Hospital,
Tirunelveli-Town.

N. C. SEKHAR,
Convener.

ANNOUNCEMENT

The Indian Medical Association, Central Office, Delhi, has invited applications for Internships and Residencies in U. S. A. and Canada for 1958. The appointments usually commence from 1st July 1958; and though they ordinarily carry a stipend the candidates will have to defray their own passage expenses. The specialities in which Internships and Residencies *may be* available are:—

1. Anesthesiology
2. Dermatology and Syphilology
3. General Surgery
4. Internal Medicine
5. Neurology
6. Obstetrics & Gynecology
7. Opthalmology
8. Orthopedic Surgery
9. Otolaryngology
10. Pathology
11. Pediatrics (children diseases)
12. Psychiatry
13. Pulmonary Diseases
14. Radiology
15. Rotating Internships (Medicine, Surgery, Midwifery, Pathology — roughly 3 months each)

Only members of the Indian Medical Association who have good knowledge and appreciation of the Indian Medical Association, its principles and workings, are eligible to apply. A copy of the Proforma in this connection and other requirements necessary and expected of those who desire to apply, may be seen in the offices of all *Local Branches of the Indian Medical Association* in the Madras State. The last date for receipt of applications by the undersigned is *15th September 1957* and all applications *must be* submitted through the Honorary Secretary of the Local Branch of I. M. A. in whose area the applicant ordinarily resides.

Dr. C. ARUMUGAM, M.B.B.S.,
Hony. Secretary, I.M.A.,
Madras State Branch.

328, Raja Street,
Coimbatore.

ADVERTISERS in the "Madras Clinical Journal" are hereby requested to send the necessary instructions and material for their advertisements not less than one month prior to the publication of their proposed advertisement. They are also requested to return the corrected proofs so as to reach on or before the date mentioned on the proof copy submitted to them for their approval. This will lighten the task and inconvenience to the advertisers would be avoided. It is hoped that advertisers will willingly coöperate with the Managing Editor.

Managing Editor.

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Complaints of non-receipt of copies should be made so as to reach the Managing Editor before the first week of the month. Is there change in your address? If there is, please inform me promptly so that you don't miss copies of "Madras Clinical Journal". While intimating change, please give your OLD as well as NEW address.

Managing Editor.