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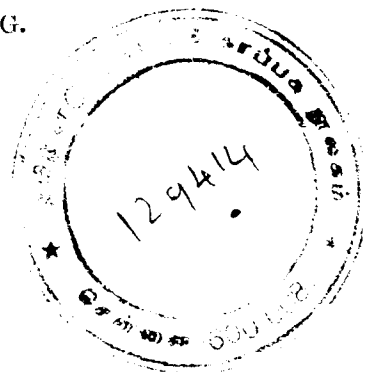
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Dr. Elizabeth Mathai Lectures.

Rheumatism in Childhood and Adolescence (As it occurs in S. India)

DR. P. KUTUMBIAH, B.A., M.D., M.R.C.P. (Lond.).

Lecture I.

Introduction.

The lectures I have the honour of delivering this and subsequent evenings were founded to commemorate the memory of Dr. Elizabeth Mathai. At the very outset I should like to express my own gratitude and that of the workers in the field of medical science for the happy thought which prompted the founders to endow a course of lectures in Medicine. Endowments for the furtherance of medical science are very few in Indian Universities. We have princely endowments in connection with arts and other sciences. But as far as medical science is concerned we have only two in this university—the present one

and the Travancore Curzon Lecture—to keep alive our flagging interest in medical science and prevent it from extinction. I should like also to compliment the founders on their wisdom in the choice of the subject for these lectures. They have laid down that these lectures should be definitely connected with some aspect of diseases of children and women. I am sure their choice reflects the wishes of Dr. Elizabeth Mathai as I can think of no wish dearer to the heart of a woman, who was a doctor herself, than the one of suffering children and women. In due deference to the wishes of the Founders I have chosen as my subject Rheumatism

CENTURIES OF USE

Medication which has been in use for centuries—in fact since the earliest recorded periods of history—and still continues to have the most wide-spread use, must be looked upon, not so much as medication that has “proved” itself, but as one of Nature’s fundamental curative measures. Reference is made to the use of *Heat*. Even in the lower animal kingdom, when disease overtakes them creatures instinctively seek the healing rays and warmth of the sun to help them to overcome their afflictions.

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which is peculiarly a disease of children and women and is the cause of great suffering, chronic invalidism and premature death among them.

Nomenclature.

Current nomenclature in the case of rheumatic disease is not satisfactory. It is often confusing and in some respects misleading. Rheumatism is a disease characterised by variable manifestations which may occur singly or in any combination; hence it is impossible to characterise the malady accurately by any one term. In its classical form with fever, migratory polyarthritis and acid sweats it is correctly designated as acute rheumatic fever. But many variations from this classical picture commonly occur; in fact these variations are sufficiently numerous as to comprise the majority of cases encountered in any large clinic where children and adults are treated. The classical form is more often seen in adults and in them cardiac complications may or may not be present. Rheumatism of childhood, on the other hand, is characterised by carditis, while fever and polyarthritis are by no means constant in this form. The term "acute rheumatic fever", therefore, fails to describe this form accurately, besides the frequent absence of fever or polyarthritis in this form may even lead to failure of recognition of many of these cases. The term "acute rheumatism" is equally unsatisfactory. Though it does not imply fever, it is almost as misleading as the term "acute

rheumatic fever", for it is now well recognised that many cases commence insidiously. Some, it is true, may eventually flare up and then become acute but recognition of the more common insidious forms is of great importance. A term, therefore, which stresses only one phase of the disease describes it imperfectly. Further, "acute rheumatism" presumes the existence of a "chronic rheumatism" etiologically connected with and as a later phase of the disease, regarding the existence of which there is a difference of opinion. Rheumatic infection is gradually coming to be regarded as a disease of childhood with less frequent and atypical manifestations occurring in adult life. This belief has prompted some authorities to term rheumatic infection as "rheumatism in childhood" or "juvenile rheumatism". Even these terms are not wholly satisfactory as rheumatic infection may occur for the first time in adult life or, as it is more common, juvenile rheumatism may continue into adult life.

Unnecessary confusion has been caused, in my opinion, by the introduction of the concept of chronic rheumatism in the study of rheumatic infection. Chronic rheumatism comprises two big groups—the fibrositic and the chronic arthritic. The fibrositic group includes muscular rheumatism, lumbago, sciatica and brachial neuritis and the chronic arthritic group includes rheumatoid arthritis, osteoarthritis, gout and unclassified arthritis. The

relationship of the fibrositic group to rheumatism is very obscure but there are many affinities between the chronic arthritic group and rheumatism. The concept of chronic arthritis as a constitutional disease like rheumatic infection rather than one of the joints alone is steadily gaining ground. It is generally conceded that there are many initiating and contributory causes in chronic arthritis. These include infection, trauma, age, heredity, disturbances of vascular supply or of general and local nutrition and metabolic or glandular dysfunction. There is still disagreement as to whether the two great groups—the atrophic (rheumatoid) and hypertrophic (osteo) arthritis—which constitute the bulk of the arthritic group represent separate clinical entities. Some hold that hypertrophic arthritis is an entity, whatever decision may be arrived at as to the nature of the atrophic form and others are firm in support of the clinical entity of the atrophic group. It seems to be generally agreed, however, that evidences of the effects of infection are much more clear in atrophic, than in hypertrophic arthritis. During the past century there has been considerable controversy over the relationship between rheumatic fever and rheumatoid arthritis. Opinion was more or less divided into two schools, those who believed that the two were separate and distinct diseases and those who maintained that they were different expressions of the same fundamental process. At the present time the majority of clinicians in England,

America and in Europe consider these two clinical entities as distinct diseases having little or no relation with one another. Occasionally, however, the opinion is still expressed that the two are intimately related and possibly different manifestations of the same process. However much it may be desirable to bring under one concept all the affections of the joints in a study of arthritis, it is unnecessary to do so in a study of rheumatic infection. Rheumatic infection is a constitutional disease affecting the heart, the joints, the brain and other parts of the body and it is illogical to stress one of its most inconstant and least important manifestations, *viz.*, arthritis. For the above reasons it is very desirable to follow the suggestion of Lord Dawson. "Taking for practical purposes the classification of acute and sub-acute rheumatism, non-articular rheumatism (fibrositic rheumatism) and chronic joint disease (arthritic rheumatism), I suggest that the problem would be forwarded if we were to separate the first of these from the other two. (Dawson).

Review of the Indian Literature on the subject.

Conflicting views have been expressed on the subject of the occurrence of rheumatic fever and carditis in the tropics. Some authorities have expressed the opinion that rheumatic infection hardly ever occurs in the tropics; some, while admitting that genuine cases are occasionally seen in the tropics, believe that the incidence is very low, the

manifestations very mild, and the sequelae less virulent. Lastly, there are others who maintain that the incidence, manifestations, and sequelae scarcely differ from what is seen in non-tropical countries (temperate climates). Those who maintain that rheumatic infection hardly ever occurs in the tropics base their assertion on the extreme paucity of any studies on rheumatism in the medical literature on diseases in the tropics and in particular in Indian medical literature and also on the rarity of cases of rheumatic carditis and mitral stenosis in the post-mortem room. Rogers (1925) expressed the opinion that rheumatic endocarditis is quite absent in India, although streptococcal infections are otherwise frequent. He came across only one case of rheumatic carditis in 4800 post-mortems carried out in Calcutta over a period of 37 years. Clarke (1930) maintained that there is no rheumatic infection in the tropics *i.e.*, in the area which lies between 23° and 28° north and south of the equator. Referring to India he says, "It can hardly be accepted that rheumatic fever occurs in a country where mitral stenosis is never found in the post-mortem room". Until a decade ago the prevalence of rheumatic infection, particularly rheumatic heart disease, was considered to be rare even by the medical men in India. Ever since 1930 there has been a growing volume of literature on the occurrence of rheumatic heart disease in India. Hughes and Yusuf (1930) reported 24 cases of cardiac rheumatism from Lahore. They came to the

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conclusion that, in the Punjab rheumatism is an important cause of valvular heart disease especially mitral stenosis. Stott (1930) from Lucknow reported 20 cases of chronic heart failure in young Indian males, mostly between 12 and 18 years of age following progressive stenosis of the mitral valve. Hodges (1932) from Jalpaiguri, Bengal, reported 8 cases under 12 years of age showing the rare features of rheumatic infection. He stated, "there seems to be ample evidence, that, as far as India is concerned, rheumatic infection is by no means rare and is a potent factor in the production of heart disease." Banerjee (1935) reported a further series of 25 cases of rheumatic heart disease in childhood from Bengal. Rheumatic infection was found by him to play an important role in the causation of heart disease in India. About one-third (33·2 per cent.) of all cases of organic heart disease in his series had a rheumatic etiology. Mangalik and Stott (1938) and Stott (1938) published critical studies on the incidence of rheumatic infection in India, particularly from Agra and Lucknow. Clarke has objected to the above evidence on the ground that the Punjab, the United Provinces and Bengal are not situated in the tropics but to the north of this limit. Evidence as to the occurrence of rheumatic infection in Tropical India is also now available. Kamath (1931) stated that classical rheumatic fever was rare but if the presence of mitral stenosis is to be taken as an index as to the existence of rheumatic infection then the condition is common

Rheumatism in Childhood and Adolescence

in South India. Kutumbiah (1935) published a study of the incidence of rheumatic infection in Vizagapatam with a critical report of 50 cases of rheumatism in childhood. He found that cases of rheumatic infection formed 3 per cent. of the total admissions into the hospital medical wards and about 43 per cent. of the total cardiac cases. He further found that in its essential manifestations rheumatism in childhood closely resembled juvenile rheumatism in the temperate climates. In a further study on the lesions in rheumatic heart disease in South India (1940) he presented the necessary histo-pathological evidence, derived from autopsies conducted in South India on rheumatic subjects, to establish the incidence of rheumatic infection in South India and so in the tropics. Fernando (1939) published a study of rheumatic heart disease based on clinical and autopsy records as met with in hospital practice in Ceylon. He found that cases of rheumatic infection constituted 1·4 per cent. of the total admissions and 21·5 per cent. of the cardio-vascular admissions. He further concluded that the incidence, manifestations, virulence, and progressiveness of rheumatic carditis scarcely differed in any important respects from what is seen in non-tropical countries.

The Theme of the Lectures.

The above review of the available Indian medical literature ought to convince even the confirmed sceptic of the prevalence of rheumatism in Tropical India. The theme of

these lectures is not to prove this already established fact. Hitherto the study of rheumatism has been based on the assumption that it does not exist in the tropics. As a result of this assumption attention has been focussed on those features in the internal and external environment of the rheumatic subjects which are peculiar to non-tropical climates. Thus Swift (1936) remarks that upon first glance the placing of rheumatic children in a tropical environment where they do not suffer from severe streptococcal infection would appear to offer useful prophylactic conditions. But the knowledge of the prevalence of rheumatism in a tropical environment should lead us to review anew the environmental factors which have been hitherto held to be responsible for the production of rheumatism and re-assess their value and incidentally discover any new facts which may modify the existing beliefs. The prime object of these lectures is to critically survey the available Indian material with a view to discover what light, if any, it throws on the nature of rheumatism. A second object is to bring home to the profession and the public at large in India, the far-reaching importance of rheumatic infection. I have a feeling that the medical profession has not as yet realised the extent and gravity of rheumatism in childhood. It is the most important and frequent cause of organic heart disease and if it can be prevented or minimised there will result from it the most

promising advance in cardiac therapeutics in our generation and a notable contribution towards national health. With these objects in view, I propose to present in these lectures a summary of the studies which have occupied over 10 years, both for the help of those who would like to know how the matter stands at the present day in S. India and also perhaps for the guidance of some who would like to investigate all the as yet unexplored areas of this field of medicine.

It is interesting to compare these figures with those of Ceylon, the other tropical country from where statistics are available. Here the rheumatic cases were found to be 2.2 per cent. of the total medical admissions and the incidence of rheumatic carditis was found to be 21.5 per cent. of the cardio-vascular admissions. The corresponding figures for Vizagapatam were 3.5 per cent. and 39.5 per cent. respectively. The incidence in percentage for non-tropical countries of rheumatic heart cases to other

TABLE I.

	Total Admissions	Total Cardiac cases	Total Rheumatic cardiac cases	Total Rheumatic cases	Percent-age 1 and 2	Percent-age 2 and 3	Percent-age 1 and 3	Percent-age 1 and 4
	1	2	3	4				
Males ...	9347	760	253	265	8.13	33.2	2.7	2.8
Females ...	3403	395	179	182	11.6	45.3	5.2	5.3
	12750	1155	432	457	9	39.5	3.4	3.5

Incidence.

During the period between 1932-1938, 12,750 patients were admitted into the medical wards. Of this number the cardiac cases totalled 1155 and the rheumatic cases 457. Twenty-five of the rheumatic group were cases of acute rheumatic fever of the classical type with no cardiac involvement. The following table gives the number of cases admitted into the medical wards, the number of cases of rheumatic infection and of rheumatic heart disease, the number of cardiac cases due to other causes, and their relative percentages.

cardiac cases is 40 for England (Lewis) and 32 for private cases and 54 for hospital cases for America (White). From the above it is evident that the incidence of rheumatism in Vizagapatam is almost as high as in non-tropical countries.

Conditions predisposing to Rheumatic Infection.

Race.

Most of our knowledge of rheumatic infection comes from Great Britain, Scandinavia,

Age.

France, Germany, North America and Australia. There have been few studies on rheumatic infection from India, China and Africa. Hence it came to be presumed that rheumatic infection is rare in these countries. The above statistics from Vizagapatam and Ceylon, both situated well in the tropics, prove this assumption is not correct. The inhabitants of India and Ceylon seem to be as susceptible as the inhabitants of the non-tropical countries to rheumatic infection. There are no studies with regard to the incidence of rheumatism among the Chinese and Negroes in Africa. The Negroes of North America are not exempt from rheumatism. It would be interesting to have a survey of the incidence of rheumatic infection among the Europeans residing in the tropics and among the Indians residing in countries where rheumatism is acceptedly common to assess their relative individual susceptibilities. The new data from the tropics throw doubt on the belief that race has influence on rheumatic infection.

According to Glover the incidence of acute rheumatism is peculiar in that it is very low before the age of five, rises to a maximum some where about the age of puberty, and then falls, the fall becoming more marked after the age of 30. Carey Coombs gives further details about the age distribution. About 66 per cent. of the total fall between the ages of 5 and 15. The decade of adolescence to the end of the 25th year accounted for another 15 per cent. Those in whom no rheumatic phenomenon was observed until after the 25th year numbered only about 10 per cent. of the total. It is clear, therefore, that it is during the childhood stage—the stage during which the body is learning to immunise itself and to limit its invasions by bacteria—that rheumatic infection of the heart is most apt to occur. The following table gives the age and the sex distribution of the 457 cases of rheumatic infection on which this survey is based.

TABLE II.

Age.	Cardiac cases.		Total.	Rheumatic cases.		
	M.	W.		M.	W.	Total.
3-5	1	6	7	1	2	3
6-10	32	20	52	0	1	1
11-15	52	21	73	1	5	6
16-20	54	42	96	6	2	8
21-25	33	36	69	1	2	3
26-30	35	30	65	0	0	0
31-35	23	12	35	0	0	0
36-40	13	10	23	1	1	2
41-45	3	1	4	0	0	0
46-50	4	1	5	2	0	2
51-55	3	0	3	0	0	0
	253	179	432	12	13	25

From the above table it is seen that the incidence of rheumatic infection is very low in the age period 3—5, rises to a maximum before the age of 25 and then begins to fall, the fall becoming more rapid after the age of 30. This is in conformity with the generalisation of Glover. But there are some notable differences from the figures given by Coombs. Only 31 per cent. of the total number fall between the age group 3—15. The decade of adolescence to the end of 25 years accounts for about 38 per cent. and in the age period between 26 and 40 there are about 27 per cent. The greatest number was found in the age group 16—20, namely 96 cases. If correct histories were available there is no doubt a good number of these cases would be found to have contracted rheumatic infection at least a few years earlier and would fall in the age group 3—15. Even after making due allowance for this fact some explanation must still be found for the considerable number of cases in the age group 21—40. It is rare to come across cases of rheumatic carditis in this period. Most of the cases come under observation with signs of cardiac disease unmistakably rheumatic in type and as unmistakably of some years standing. It is also generally conceded that when rheumatic infection occurs for the first time in an adult it produces acute rheumatic fever of the classical type in which the heart generally escapes. So the cases seen in this period must be either cases of cardiac rheumatism which have not succumbed in childhood

but have survived with healed and scarred lesions producing well recognised rheumatic cardiac lesions like mitral stenosis or they must be cases of an insidious form of cardiac rheumatism in which permanent cicatricial deformity like mitral stenosis was established without the intervention of a clinically acute state. As Swift remarks, "one should also recall the tendency for rheumatic manifestations to recur, especially during childhood, while after puberty this tendency decreases. Puberty indeed seems to constitute an important and critical stage in the life of the rheumatic youth. If, because of previous damage his heart has undergone marked hypertrophy and is unable to meet the demands of rapid bodily growth, resulting failure soon terminates the picture. If, on the other hand, the child has sufficient reserve to pass this critical period, he will probably live through succeeding years with distinctly fewer rheumatic relapses than he suffered before the age of puberty." The devastating effect of relapses on the heart is well recognised. Survival into the decade of adolescence entirely depends on the severity of the initial infection of the heart and the frequency of relapses. If the initial attack is mild and the relapses infrequent then there is every likelihood of the subject entering into the period of adolescence, it may be with a cardiac defect. That the above interpretation is correct is shown by a study of the incidence of mortality in the different age periods. Table III gives these details.

TABLE III.

Age.	Cardiac Cases.		Deaths.	
	M	F	M	F
3-5	1	6	0	0
6-10	32	20	1	0
11-15	52	21	7	1
16-20	54	42	8	6
21-25	33	36	3	3
26-30	35	30	0	9
31-35	23	12	3	2
36-40	13	10	1	0
41-45	3	1	0	0
46-50	4	1	1	0
51-55	3	0	0	0
	253	179	24	21

From this table it will be seen that the total number of deaths was 45. In the period between 3—15 there were 9; in the period between 16—25 there were 20; in the period between 26—35 there were 14; and in the period between 36—45 there was one. The death rate for the period of childhood was 20 per cent.; that for the decade of adolescence was 44·4 per cent.; the death rate for the next decade was 31 per cent. After that there was a marked fall to 4 per cent. This clearly proves that about 80 per cent. of cases survive the childhood period and of those who survive 55 per cent. die in the decade of adolescence emphasising the killing effect of puberty on rheumatic youth. After this, the death rate rapidly falls. It may be noted that almost all the cases after the decade of adolescence are clinically inactive cases of chronic valvular disease of the typical rheumatic variety in whom death was brought about presumably not by the rheumatic infection but by the mechanical defects established by the infection resulting in cardiac defect.

Sex

The distribution according to sex is also interesting as at all age periods the males were more numerous than the females except in the age period 21—25 in which the females slightly outnumbered the males. These figures rather overstate the sex factor. The total number of female admissions formed only 36 per cent. of the male admissions. But compared with the total number of male rheumatic cases the female rheumatic cases formed 76 per cent. When the percentage of rheumatic cases to total admissions is taken, that of the males works out to 2·7 per cent. of the male medical admissions whereas that of the females is found to be 5·2 per cent. of the total female medical admissions. The male rheumatic cases formed 2 per cent. of the total medical admissions, whereas the female rheumatic cases formed 1·5 per cent. Besides one has to take into account the total male and female populations in the district. Unfortunately I am not able to get the exact figures with regard to sex distribution of the population in

Vizagapatam. From the above considerations it is clear that rheumatic infection is much more liable to attack females. This is in conformity with the sex distribution of the diseases in other countries. But the incidence in the males is certainly very much higher than one suspects.

Heredity.

It has long been held that rheumatic fever is a markedly familial disease. Because of the importance of this aspect of the problem particular attention was paid to the family history of the patients of the above series of cases. The difficulties are admittedly great. It is difficult to get the history of even the patient correctly with regard to the various rheumatic manifestations to say nothing of the other members of the family. However the results of this inquiry lend no support to the existence of a familial factor. A familial history was obtained in seven cases only. In three of these cases either a brother or sister had similar heart trouble. In one, three brothers were supposed to suffer from heart disease. In one, the father's cousin died of similar heart trouble. In the remaining two either the father or mother had similar complaint. In not one of these cases the facts could be verified. I have only seen one instance in which a sister and a brother were affected—the brother with mitral stenosis and regurgitation, and the sister with mitral stenosis. Dr. Venkatagiri of the Madras Medical Service has provided me with another instance where two

members of a family had mitral stenosis, a brother and a sister. Banerje (1935) found in 6 out of 25 of his cases that some brothers or sisters had either died of rheumatic heart disease in childhood or had been suffering from the same at the time of the investigation. The results of the present inquiry is in marked variance with the results of the western authorities. Coombs found out of 178 histories 13 were indeterminate; of the remaining 165, 82 were positive, and 83 negative. Cheadle in his records of 180 cases of rheumatic infection in childhood, seen in private practice, found evidences of the hereditary factor in 103. The American statistics of familial incidence varies between 37 to 50 per cent.

Contagion.

It has been argued that the mass incidence of rheumatism among children may be due to case to case infection. In this series of 457 cases, there was only one instance where a history was obtained of more than one member of the family suffering from the disease. In that case three elder brothers were said to have been affected by rheumatic heart disease. Barring this one instance there was no other evidence to show that infection from case to case could have been operating. I have not come across any case of rheumatic infection taking place in the hospital where for the past ten years one or more cases were always in the wards. Neither have I come across an instance of a child born to a mother suffering from rheumatic

heart disease and showing evidence of rheumatic infection. In the few post-mortems done on premature and till born children in our hospital there has not been one instance of foetal endocarditis. Rheumatic infection is extremely rare below the age of five years. Below this age I have had only two instances of rheumatic infection and both were in children of three years of age, and there was no case below that age. From these data there is no evidence of any direct transmission of the rheumatic agent from the mother to the child or for the infection being communicated from one child to another child. The theory that rheumatic infection may be spread by contagion has very slender foundation.

The influence of environment on Rheumatic Infection.

"Among the present day problems of juvenile rheumatism there is, in my opinion, none worthier of an accurate study than that of the influence of environment on the large scale production of the disease. My reason for insisting on the pre-eminence of this particular question is that, as the position appears today, in our efforts to prevent and control the disease in this country (England), we have a better chance of success by getting to work on environmental influences than by other means". These remarks of Miller (1925) made at the Bath Conference are as true today and as applicable to conditions in India as it was in the year it was uttered as to conditions prevailing in England. It

might be asked in what way can environment influence the course of an infectious disease. In the strict sense of the term, environment cannot be regarded as the cause of any infectious disease. But there are many ways in which environment can influence the course of an infectious disease indirectly. As far as the infecting organism is concerned, it may lead to increased virulence of the bacterial agent, and as far as the person is concerned it may lead to a diminished resistance in him or to the development of some abnormal condition which, in its turn may act as a preliminary to the infection in question. It may also work more frequently and more powerfully in another way, namely, by stimulating and unmasking an infection already latent, turning it from a mild to a severe attack. "The cause of acute rheumatism is not yet fully proved but the hypothesis which at present holds the field is that acute rheumatism is the reaction of the human body to the presence of the streptococcus viridans. This organism is widely distributed, is frequently found as a harmless saprophyte or as the causal agent in lesions which have nothing to do with rheumatic fever. If it be, as it is believed, a common, perhaps a constant, inhabitant of the body, we must concentrate our attention on the conditions, circumstances, or predispositions external or internal which influence it to assume an activity which results in rheumatic fever. It would appear to be as futile to attempt to annihilate this streptococcus as it would be to exterminate the bacillus of tuberculosis,

Our attack upon either of these diseases we must direct our main efforts to the fortification of the human body, to the exclusion from it of the invading micro-organism, or the frustration of the activities of the micro-organism within the human body. This largely resolves itself into a question of those social conditions of the child which lead to rheumatic infection." So remarks Sir George Newman in his presidential address to the Bath Conference in 1928. In the decade that has since passed our knowledge about the causation of acute rheumatism has been much advanced. We have begun to appreciate the part played by the hæmolytic streptococci in connection with acute rheumatism. Much light has been thrown also by the recent researches as to the nature of the tissue reaction of the human body to the presence of the streptococci. The tissue of rheumatic patients appears to be unusually vulnerable to several injurious agents and especially to substances contained in or derived from, streptococci. We are beginning more and more to realise the relationship between allergy and rheumatic fever. The failure of the streptococcal and allergic theories to explain completely and satisfactorily the pathogenesis of rheumatic fever has led many workers to the opinion that the disease is due to an undiscovered filterable virus, while others have advanced the concept that rheumatic fever may be the result of the combined influence of Vitamin C deficiency and infection. While much of the newer knowledge about the

disease still lacks confirmation the contention of Miller and Newman that environment plays a profound role on the many initiating and contributory causes of acute rheumatism remains firm and unshaken.

The environmental factors which are at work in the large scale production of rheumatic infection are (1) climatic and seasonal influences (2) poverty (3) urbanisation and industrialisation (4) school environment (5) diet and nutrition (6) damp and cold. I propose to dwell at some length on each of these factors to discover the part they play in the production of rheumatism as it occurs in South India.

Climate and Seasonal Influences.

Very little is known as to the geographic distribution of rheumatic fever and rheumatic heart disease in India. We have valuable studies on the subject for United States by Nichol (1936). This study reveals that there is a definite inequality in the distribution of rheumatic fever and rheumatic heart disease in the United States, the amount being much less in the Southern States. Only 2 per cent. of "cardiac" patients found in Miami situated 25° Lat. N. in the Southern States had rheumatic heart disease compared with 39.8 per cent. of cardiac patients encountered at Boston situated 42° Lat. N. in the Northern States. Longcope discussing the variations in the manifestations of rheumatic fever in relation to climate emphasised that arthritic

manifestations of rheumatic fever are less outspoken in Baltimore situated 39° Lat. N. compared with cities further North and in the latter locality it is essentially a disease of the heart of a rather insidious type. These observations are extremely interesting. Vizagapatam is situated in Lat. 17°42' N. Here rheumatic heart diseases formed 39.5 per cent. of hospitalised "cardiac" patients. Whereas the figure for the same at Boston situated 42° Lat. N. is 39.8. Baltimore is situated 39° Lat. N. Yet in Vizagapatam, as in Baltimore, the arthritic manifestations of rheumatic fever are less outspoken and rheumatic infection is essentially a disease of the heart of a rather insidious type. Of the 457 cases of rheumatic infection in hospitalised patients only 25 cases were cases of acute rheumatic fever of the classical type and the remainder 432 were cases of rheumatic heart disease of a

rather insidious type. Ceylon lies between 5° 55' and 9° 50' Lat. N. Here out of 215 rheumatic cases 71 were found to be cases of rheumatic fever alone and 143 were rheumatic heart cases. Here rheumatic heart cases formed 21.5 per cent. of the hospitalised cardiac patients. Bengal is situated between 22° Lat. N. and 26° Lat. N. Here the incidence of rheumatic heart disease was 33.2 per cent. of total "cardiac" cases both hospital and private. These figures make one doubt whether geographical position in terms of latitude alone has any influence on the incidence of rheumatic infection. Other characteristics of climate and season must also be taken into consideration *viz.*, temperature and its variations, humidity and rainfall and the prevailing winds. The following tables give the available meteorological data for Vizagapatam.

TABLE IV
Average during the decade 1913—1922.

Months.	Normal Maximum.	Normal Minimum.	Mean.
January	81.1	67.9	74.5
February	83.6	71.0	77.3
March	87.4	74.5	80.9
April	89.4	78.2	83.8
May	91.6	80.5	81.0
June	91.4	79.9	85.6
July	89.1	78.4	83.7
August	88.8	78.1	83.4
September	88.3	77.9	83.1
October	87.6	76.2	81.9
November	84.4	72.5	78.4
December	81.0	68.1	74.5
Annual	87.0	75.0	81.0

It would be seen from the above table that the temperature is fairly steady and varies within narrow limits not only throughout the day but also throughout the months and even throughout the year. The summer temperatures are considerably lower than those in Madras and the Ceded Districts. The minimum temperature in winter rarely falls to 60°F. The diurnal range is about 12 degrees to 15 degrees and the variations during the year confined to a range between 65° to 95°F. One may therefore state that it is neither the high temperatures of summer nor the low temperatures of winter that determine the incidence of rheumatic infection at Vizagapatam. Vizagapatam town is, on the other hand, characterised by a steady and stable temperature throughout the year with a narrow range of daily variation. Table V gives the relative humidity in the different months of the year.

TABLE V.

Months.	Relative Humidity.
January	72
February	73
March	73
April	71
May	71
June	74
July	78
August	87
September	79
October	74
November	65
December	63
Mean	73

The most moist part of the year is the middle of August and the driest is the middle of December.

The average humidity is uniformly high. Table VI gives the average rainfall.

TABLE VI.

Months.	Mean Monthly total.	Mean number of days.
January	0.46	0.5
February	0.85	0.9
March	0.30	0.5
April	0.71	1.6
May	1.99	3.0
June	4.86	6.8
July	4.49	8.4
August	5.36	8.4
September	6.52	8.5
October	7.07	7.3
November	3.75	4.0
December	0.73	1.0
	37.09	

It is very difficult to estimate the seasonal incidence of rheumatic infection. Data with regard to the date of the first infection is often difficult to get in cases of rheumatic heart disease. It is only in the case of acute rheumatic fever that correct data as to the onset of the symptoms is possible. As remarked above, cases of classical acute rheumatic fever are very rare in the wards. A survey as to the incidence of these few cases reveals no marked seasonal variation. In July there were no cases of rheumatic fever. In October the largest number of 8 cases occurred. In all other months there were 3 or 4 cases. Of course the number is too small to arrive at any definite conclusion. Even in these few instances no correlation could be seen between the temperature, humidity and rainfall.

The only other tropical country from where exact meteorological data is available is Ceylon.

Ceylon lies between 5° 55 and 9° 50 Lat. N. The annual mean temperature along the coast is 80° F. and a noteworthy feature is the smallness of the variation both between day and night temperatures in the same 24 hours and during different parts of the year. Everywhere in Ceylon there is a relatively high degree of humidity; the average percentage varies little from month to month. During the South West monsoon the relative humidity by day is usually well over 70 per cent. in the wet zone and at night owing to the fall in temperature it is about 90 per cent. Even in dry zone the average humidity in any month rarely falls below 60 per cent. Ceylon may be divided into a wet zone and a dry zone. Over the wet zone the average annual rainfall is more than 100 inches and in places reaches 200 inches. In the dry zone the average rainfall is less than 75 inches per annum. Here there are large tracts with annual averages of less than 30 inches.

There is a remarkably close resemblance as regards the temperature and humidity conditions between Ceylon and Vizagapatam. In both the mean annual temperature is roughly about 80 per cent. The humidity during the South West monsoon varies between 74 and 87 per cent. and during the North East monsoon between 74 to 63 per cent. There are only two months, November and December, when the humidity is 65 and 63 per cent. respectively. In all other months the humidity is

above 70. The mean humidity for the year works out to be 73. With regard to rainfall Vizagapatam resembles the dry zone of Ceylon. The average rainfall even in the best years scarcely reaches 40 inches. The normal average being 37 inches. Even with this remarkably close similarity in the meteorological conditions of these two places there is a marked difference in the incidence of rheumatic fever and rheumatic heart disease. Roughly the incidence of rheumatic heart disease is about two times greater in Vizagapatam than Ceylon. The incidence of acute rheumatic fever is greater in Ceylon and works out to three times that of Vizagapatam.

In non-tropical countries it is considered that some relationship exists between high rheumatic incidence and low rainfall and high monthly mean temperature. Even in these countries there is a difference in the incidence of rheumatic heart disease in various localities. Even here no precise correlation can be made out between the incidence of rheumatic infection and the variations in climate and season. Summing up the influence of climate and season on rheumatic infection in the tropics, no definite decision as to whether the conditions of temperature rainfall and humidity have any marked influence in determining the incidence of rheumatic infection here can be arrived. The remarks of Coombs with regard to the geographical distribution of rheumatic infection express in very cautious terms our present knowledge on the subject. "Broadly,

it is found in temperate climates only; but whether this is owing to the conditions of temperature and rainfall, to the distribution of the various races of mankind, or to the economic conditions that prevail in such climates does not appear obvious. The data on which a reliable opinion could be found are not yet available." To the above remarks, we may add, it is also found in the tropics and here too the same difficulty exists in forming any reliable opinion on the data available.

Poverty.

Rheumatic infection is often called a "poverty disease". This designation is rather unfortunate, as it gives one the impression that were poverty to be removed, there would be no rheumatic infection. In fact Miller does express such an opinion. "It is clear that were there no poverty there would be practically no rheumatism problem in children." But this view is not borne out by our study. A scrutiny both of the in-patient and out-patient statistics reveals that rheumatic infection is not very prevalent in the really poor, namely, the destitute, the starved and the dwellers of the slums. A very great percentage of our rheumatic patients belong to the middle classes and even in this to the middle and upper strata of this class. Clerks, teachers, petty merchants, pupils of elementary and secondary schools and students of colleges form the bulk of our rheumatic cases. In private practice one comes across many cases of rheumatic infection in the children of the upper middle classes and the

rich. The line dividing the poor, the middle and the rich classes is very arbitrary and difficult to define in India. The very rich are very few and their children are pampered and by no means very healthy. It is correct to say that the rheumatic stratum of society runs through the middle of the middle classes. Our experience in the hospital wards fully bears out the verdict of the Medical Research Council, "If the hospital patients are divided into three classes according to the degrees of poverty, the poorest of these three, the very poor and destitute, show a lower incidence of rheumatism than the other two", but with this proviso that the standards of poverty vary considerably in both countries.

Urbanisation and Industrialisation.

In a general way it may be stated that rheumatic infection is a disease of the towns rather than of rural areas. Very little data is available with regard to the prevalence of rheumatic infection in our villages, small towns, big cities and industrial centres. Those who have had a fairly long experience of the city hospitals would be impressed at the remarkable increase in rheumatic disease during the last decade or two. This may be due to many factors not the least of these being the growing concentration of the population in towns and cities and industrial areas. This process is still on the increase. It is permissible to infer that the recently noted increase in the incidence of rheumatic infection may be due

to this urbanisation and industrialisation of our population. Whether it is due to overcrowding in the towns and cities and industrial areas or to the poor housing conditions that prevail in these areas, or to the stress and strain of town life, it is difficult to say without reliable and extensive data with regard to the incidence of rheumatic infection in our villages and towns.

School Environment.

I have been impressed with the incidence of rheumatic infection in the school-going population of our towns. Both in private practice and in hospital work, I have come across a good number of cases of rheumatic infection in children attending various schools in the city. It is difficult to exactly discover the factors in the school environment that predispose the child to rheumatic infection. There is a remarkable coincidence between the number of cases of tonsillitis and rheumatic infection which one sees in this class of children. What actually contributes to this increase of tonsillar inflammation in the school environment is difficult to say. Lack of proper ventilation, sunlight, and other hygienic conditions do not appear to be the sole cause. It must be attributed to the strain imposed on the child by the school regimen. The tedious hours of work, the very few intervals that are available for rest, the insufficient recreation and above all the pernicious habit of prescribing home work to the children outside school hours are, in my opinion, contributory factors in

the production of rheumatic infection in children. It is not only the school environment that is at fault. The environment at home also is to be blamed. Home work robs the child of the peace and rest that are so essential for their well being outside the school hours of work. There is an urgent necessity to critically examine the factors that contribute to the remarkable increase of rheumatic infection in the school going children. A survey of the whole population of the elementary and secondary schools and colleges with regard to the incidence of infected tonsils and early signs of cardiac rheumatism is very urgently needed.

Diet and Nutrition.

It is difficult to estimate the precise part which diet plays with regard to rheumatic infection. It is not the under-nourished child that is frequently the victim of rheumatic infection. It is quite true that many cases of rheumatic infection in children are underweight; this is the result of the disease and not the cause of the disease. We have already seen that poverty as such does not contribute materially to the production of rheumatic infection. The fault in diet is not so much quantitative as qualitative. Unbalanced diet or diets deficient in vital constituents may perhaps play a part in the production of the disease. Even in these cases their influence must be very indirect. Gastric disorders and other intestinal derangements by undermining the powers of assimilation of the child may be the contributory

factors. I am unable to arrive at any definite relationship between diet and nutrition and the prevalence of rheumatic infection in South India.

Damp and Cold.

There has been much discussion as to the part played by damp and cold in the production of juvenile rheumatism. "Some affect to regard this as a mere bogey; others think that they work merely by a lowering of resistance and have no particular relationship to rheumatic infection." Miller, on the other hand regards damp as the greatest ally of poverty in producing rheumatism and heart disease in children particularly damp associated with cold. The influence of these two factors in the production of rheumatic infection in Vizagapatam cannot be very great. As has been shown above the rainy season here is from June to November but even in this season the rainfall is capricious. For years the rainfall is confined to only three months in the year. Dampness of the dwelling places is not a very common feature as the major part of the year is comparatively free from rain. The two months during which the lowest temperatures prevail viz., December and January are the two months which are particularly free from any rain. On the other hand the rainy season is marked by the prevalence of high winds. During the rainy months

particularly when high winds prevail, a sharp rise in infection of the respiratory tract is noted. The part played by infection of the upper respiratory tract in the production of rheumatic infection is well recognised and will be discussed in greater detail in the next lecture. From the above considerations, it will be seen that damp and cold as such have no direct influence on the production of rheumatic infection in Vizagapatam but they indirectly predispose to infections of the respiratory tract and thus may play a part in the production of rheumatic infection.

"Very much remains to be proved, however. What is it that gives the family factor, urban life, and the climate, the effect that they have? And on what do they operate? On the tonsillar defences solely, or on the tissue of the heart also? Much remains unsettled, merely because the evidence has never been collected. There is urgent need for co-operative research into the conditions under which rheumatic heart disease arises and it is devoutly to be hoped that when it is undertaken it will be on a scale that will take account of all the factors—the incidence of the disease in its relation to geography, to species, to race, to economics—on a scale such as has enabled pathologists to gain the comprehensive picture which we now possess of the place of tuberculosis in the world." (Coombs).

Burns

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Accidents due to burns are common to meet with, in general practice, though they are not so frequent as in centres in the west where people are exposed to colliery explosions. Most of the cases that come under the care of the general practitioner are due to the clothes catching fire or due to scalds. During the course of four months commencing from October 1939, 11 cases were admitted in different stages into the First Surgeon's wards of the King George Hospital and in most of them I tried the treatment advocated by Bettman which consists of coagulating the burnt area with tannic acid and silver nitrate. The results are encouraging.

Before I proceed with the treatment of burns according to this technique, a consideration of the pathology of burns and the clinical features is not out of place as the rationale of the treatment can be better appreciated after considering the several changes that take place in the body and the complications that may arise in untreated cases.

Wilson in a close study of 65 cases of burns has brought out the relationship between the several stages that are seen in the clinical course and the

sequence of the pathological effects of burns. According to him the clinical course is divided into five stages:—

- (1) Primary shock.
- (2) Secondary shock.
- (3) Acute toxæmia.
- (4) Septic toxæmia.
- (5) Healing.

Shock which follows burns bears a close resemblance to that after severe trauma, and the etiological factors responsible for it are the same though there is still much speculation as to the causation of shock. Primary shock is due to a disturbance in the vasomotor mechanism brought about by nociceptive impulses transmitted along the afferent nerves from the traumatised or burnt area. This occurs soon after the accident and the degree of shock depends on the extent of the surface of the body involved. It is transient and seldom lasts for more than two hours, although it may merge into secondary shock unless prompt treatment is adopted to overcome the primary shock. During this stage there is considerable fall of blood pressure, the skin is cold and pallid, temperature subnormal, pulse feeble and the patient shows apathy or anxiety. The

percentage of deaths estimated in this state is about 2 per cent.

Secondary shock supervenes soon after the primary shock or after a lapse of a short period. It progresses in spite of warmth and relief of pain to which primary shock responds. This is a common and a dangerous form of shock after burns and a good number of deaths, about 25 to 30 per cent, occur during this stage. The causation of secondary shock is not well established although several hypotheses were put forward, such as toxic absorption, painful impulses, and loss of fluid from the traumatised area. Experimental evidence is more in favour of loss of fluid by evaporation from the surface and accumulation in the tissues immediately underneath. The severity of shock depends on the extent and depth of the burns and it is most evident within 24 hours after the accident. The changes that take place during this period, as shown by post-mortem examination of fatal cases, are infiltration of the liver with eosinophile cells, the significance of which has not yet been clearly understood; fatty degeneration of epithelial cells surrounding the efferent veins of the lobules; pallor of other viscera; congestion of brain, lungs and spleen; and cedema of the subcutaneous tissues underneath the burnt area.

In the initial stages of secondary shock there is a decrease in pulse pressure due to a fall in the systolic and slight rise in the

diastolic pressure. After an interval of one to two hours a fall both in the systolic and diastolic pressures is noticed which is rapid and occasionally very pronounced. The clinical features of shock appear after the collapse of the arterial pressure has begun. The patient complains of intense thirst, the skin is pale, cold and clammy, temperature sub-normal, respirations which are not perceptibly changed in the initial shock become shallow and rapid. Vomiting is one of the constant features in this stage though not so marked as in acute toxæmia and it adds to further fluid loss. The patient may show anxiety or apathy; anxiety more commonly in adults and apathy in children.

The next stage or stage of acute toxæmia is the most dangerous period and it accounts for about 60 to 70 per cent. of deaths. It makes its appearance generally from 40 to 60 hours after the accident, although it may appear much earlier in serious cases. The causation of toxæmia has not been definitely decided. According to Underhill, it is due to the concentration and increased viscosity of blood brought about by fluid loss. Although the circulatory disturbances can be explained by Underhill's theory, the pathological changes in the various parenchymatous organs and the clinical features lend very little support to this theory. Concentration of the blood is not sufficient to explain for instance, the albuminuria which does not appear in other conditions of dehydration such as persistent

diarrhœa and prolonged vomiting. It also cannot explain the severe damage to the liver, kidney, supra-renals, etc. The second theory, that of toxæmia due to bacterial origin enumerated by Aldrich, is held by some but the failure to prepare cultures from the burnt surface in most of the cases rules out this possibility. Most of the observers hold that the toxæmia is due to absorption of product of proteolysis formed by the disintegration of the tissues at the burnt area.

During this stage there is cloudy swelling of the parenchymatous organs. The kidney, and the liver are particularly damaged showing fatty degeneration and areas of focal necrosis. The suprarenal cortex shows varying degrees of congestion and hæmorrhage with nuclear degeneration of the cortical cells. The gastric mucosa is eroded in patches. These pathological changes are more in favour of the third stage, being due to a toxic condition rather than a disturbance in blood concentration.

The stage of acute toxæmia may become evident after the secondary shock, but in severe cases, one may merge into the other. The first sign is generally vomiting which is persistent and distressing. Presence of blood in the vomit indicates the onset of a high degree of toxæmia. Simultaneously there is evidence of mental disturbance which is manifested as restlessness and irritability in children and as anxiety and delirium in adults,

which are very little influenced by ordinary dosage of sedatives. The mental condition gradually merges into stupor and finally into coma. The temperature shoots up to 103 to 104 degrees and sometimes there may be hyperpyrexia. The pulse becomes progressively rapid and feeble. The skin is cold—a striking contrast with the high rectal temperature.—It is due to failure of the peripheral circulation. The systolic pressure remains at the normal level but the pulse pressure is diminished due to a rise in the diastolic pressure. Just a few hours before death there is a rapid fall in both the systolic and diastolic pressure due to cardiac failure. The respirations are not particularly affected in the absence of any pulmonary complications. The changes in blood are not constant. There may be diminution of chlorides, due to accumulation of these in the fluid that collects underneath the burnt area. The CO₂ combining power is diminished and there may be a rise of urea and non-protein nitrogen. Mention has to be made in this connection that the sodium content of the blood is disturbed owing, probably, to the changes in the suprarenal cortex which controls the sodium metabolism. The urine shows abnormal constituents such as albumen, acetone and sometimes blood casts. Sometimes the patient may develop jaundice and this is in accord with the gross changes that take place in the liver very early in this stage. Thus the whole picture is that of a toxic condition which may be mild or severe according to the

extent and depth of the affected area. Very deep or very superficial burns are often associated with mild or no toxæmia. On the other hand burns which do not destroy the vascular dermis but expose it, produce severe toxæmia. The cause for this, as suggested by Wilson, is the ease with which the toxic products can be absorbed through the highly vascular dermis.

In cases where the extensive raw surface becomes infected the fourth stage or the stage of septic toxæmia supervenes. This becomes evident after a week and unless it closely follows the acute toxæmia, the local signs of inflammation, such as redness at the margins of the burnt surface, are evident. There is exudation of purulent discharge which collects under the tanned surface and comes out either at the edges or through cracks in the thin coagulum. The usual features of septic absorption are present. The organism that is grown from the surface is generally a hæmolytic streptococcus.

The last stage in favourable cases is the stage of healing which does not require any elaborate description except that unless care is taken, deformities occur as a result of contraction of scar tissue that forms during this stage.

Complications.—Complications of the respiratory tract are common. These are seen particularly in cases where the chest is involved. It has been said

that these complications are due to the application of heat to the chest wall, but they are seen particularly, where the patient has inhaled hot fumes when the clothing catches fire, or steam in cases of scalds. Although limitation of movements of the chest may be a contributory factor, the respiratory complications seem to be, more due to irritation of the respiratory tract by inhalation of fumes, etc.

Acute ulcer in the first part of the duodenum or gastro-enteritis is sometimes seen.

Severe collapse, restlessness which does not react to sedatives, persistent coffee ground vomiting, diarrhoea and presence of blood in urine appear in successive stages and indicate a bad prognosis.

The important features in the pathological process that have been briefly dealt with and which are so closely related with the clinical features are,

- (1) The excessive loss of fluids from the circulating blood which is most prominent during the first 24 hours after the accident. It is estimated, that in a person weighing 150 lbs., a burn involving 1/6th of the body surface may cause a loss of about 3500 c.c. of blood from active circulation, partly by evaporation from the exposed surface and partly by the shifting of blood from circulation

into the tissues underneath the traumatised area.

- (2) The absorption of toxins formed by protein lysis which causes severe damage to the liver, kidneys and suprarenals.
- (3) The occurrence of sepsis.

With these in view any rational treatment should be aimed at prevention or control of the above processes. The treatment of burns has undergone several changes. Time does not permit me to go into the details of the different methods adopted but I will make a passing mention of the treatment with oily preparation and antiseptics before I take up the modern method which aims at the formation of a thin coagulum on the injured surface. Oily preparation may relieve the pain to some extent; but do not prevent infection. They produce abundant scar tissue and prolong the period of hospitalisation. Crude Cod-liver oil which is popular in some clinics is no better than other oily preparations except for the powerful antiseptic property. When Cod-liver oil is used, the burnt surface is dressed with lint soaked in the oil and kept saturated with it for 48 hours. It is claimed that the nausea produced by the unpleasant smell passes off soon.

Among the antiseptics, 2 per cent. aqueous solution of picric acid and 1 per cent. gentian violet have been used. Picric acid is not only an antiseptic but has

coagulating properties; but it coagulates only the superficial tissues and does not penetrate.

These various kinds of treatment have an uncertain value compared with the tannic acid treatment which was first introduced by Davidson in 1925. He used tannic acid to precipitate protein with the object of fixing any toxic agent which might be formed in burnt tissues. It has later been realized that it has the additional advantage of forming a protective coagulum which prevents exudation of fluid at the injured surface. Although several changes have been made since the time of introduction of the tannic acid treatment, the principle underlying the whole treatment has been the same.

First Aid.—It had long been realised by the Chinese that decoction of tea leaves was very efficacious in the treatment of burns. Tea, as it is taken, contains 2.5 per cent. tannic acid and there can be no better first aid treatment than to apply a clean dressing soaked in tea. Oily preparations should never be used as they interfere with the subsequent treatment with tannic acid and do not prevent the exudation of fluids which is responsible for collapse. The initial or primary shock is treated by an injection of 1/4 to 1/2 gr. of morphia in adults and the application of warmth. Even in the case of children, Mitchiner advocates the administration of opiates in the form of Tinc. Campher Co or Tinc. opii in small doses. I have found rectal

paraldehyde 1 dr. in 1 ounce of gingely oil or olive oil and allonol very efficacious in children. These can be repeated if necessary.

Treatment with Tannic Acid.—

The coagulation treatment with tannic acid prevents secondary shock, acute toxæmia and septic toxæmia. When it was first introduced, solutions of 2 to 5 per cent. were used and at the present day this method has its advocates. Mitchiner prefers dilute solution and claims better penetrating power into the deeper tissues. It can be used as a spray or a compress which is periodically changed till a coagulum is formed. Since tannic acid has no antiseptic properties a further advance was made by the addition of antiseptics such as acriflavine, gentian violet and hexyl-resorcinol. Mitchiner contends that these interfere with the formation of a hard and satisfactory coagulum and that gentian violet does not mix well with tannic acid. He uses 1 in 2000 perchloride of mercury which has the additional advantage of forming a precipitate with the exudation. I find that the use of tannic acid with or without the above antiseptics (I used 1 in 1000 acriflavine) entails an extraordinarily efficient nursing and causes great discomfort for the patient by the spraying or change of compresses which should be done at intervals of 1 to 2 hours till a firm coagulum is formed which takes nearly 24 to 48 hours. At a time when the patient should be kept warm and quiet he is soaked in wet dressings and frequently disturb-

ed. Since the loss of fluid from the burnt surface is at its maximum within the first 24 hours, measures adopted to hasten the formation of a firm coagulum would be more efficient than those which take a long time. When wet solutions are supplied to tissues over a long time, it produces oedema, maceration of tissues and liability to infection. The epithelial islands which are of great importance in the epithelialisation of the injured surface are partially destroyed by the long application of any solution.

To overcome the defects of weaker solutions, a stronger solution to the extent of 20 per cent. has been used, which does not necessitate frequent spraying or changes of the compresses.

I have tried the above methods on previous occasions and although they are a distinct advance over the antiseptic and non-coagulant treatments, tannic acid and silver nitrate treatment suggested by Bettman has several advantages, which cannot be claimed by the other methods. In the series of cases that came under my care, I adopted the tannic acid silver nitrate treatment with very favourable results. Of the 11 cases that were admitted one, a child died soon after admission in the stage of secondary shock, two were admitted a week after the accident and the ulcers were treated in the usual way. The remaining 8 cases were treated with tannic acid silver nitrate, and the stages of secondary shock and acute toxæmia were successfully



This patient was in the hospital for 28 days and the clinical photo taken at the time of discharge shows the burns completely healed.



The clinical photo was taken at the time of discharge 19 days after admission for burns on the face, arms and side of the trunk.



This patient was in the hospital for 28 days. The freedom of movement at the axilla is well illustrated.



Clinical photo taken at the time of discharge. 11 days after admission before the coagulum was peeled off. He attended as an out-patient for a few days after.

Burns

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overcome. Out of these, one case, a woman of middle age admitted for extensive burns on the back and thighs, developed septic toxæmia and died 2 weeks after the accident. This patient was restless in spite of the sedatives used and on account of the wriggling in bed, the thin coagulum came off in portions and exposed the raw surface to infection. In the second case the patient developed broncho-pneumonia and died after getting over the stages of shock and toxæmia. The third case, as a girl about 8 years old, admitted for burns of third degree on the chest and arms, and fourth degree on the face. The patient was discharged after prolonged hospitalisation due to sepsis and very slow healing process (Photo No. 1). The remaining five were discharged without any complications, the minimum period of hospitalisation being 11 days and maximum period being 28 days. (See figures 2 and 5).

Before I enumerate the advantages claimed for the tannic acid silver nitrate treatment, I shall briefly describe the technique adopted by me.

Tannic Acid Silver Nitrate treatment.—The patient is given an anæsthetic, preferably gas and oxygen. Blebs are cut, the loose epithelium is removed and the injured surface is cleaned with swabs soaked in soft soap solution avoiding any irritants but generally by the time the patient is brought to the hospital it is contaminated with dirty clothing in which case I use dilute solution of ether soap. This removes all

dirt, grease and the dead and loose epithelium. The surface is then cleaned with swabs soaked in sterile water and dried up completely with gauze. To this clean surface sterile freshly prepared 5 per cent. solution of tannic acid is applied with swabs soaked in it. This is repeated twice or thrice drying up the surface each time by directing warm air from an electric hair drier. Where the hair drier is not available, a foot bellows serves the purpose and it gives a good current of air which can be made warm by passing it through a coiled tube immersed in hot water. The tannic acid produces a thin greyish precipitate. The surface is subsequently touched once or twice with swabs soaked in 10 per cent. solution of silver nitrate and dried up in the same manner. The silver nitrate combines with the precipitate and instantly turns it black, a thin pliable coagulum being formed. It is very essential that it should be absolutely dry, as any moisture left underneath leaves a raw surface which becomes evident when the coagulum is subsequently removed. The whole process, even in extensive burns, takes less than 45 minutes. No dressing is generally needed but in cases where the trunk is involved, a dry dressing will prevent the removal of the coagulum which sometimes occurs when the patient is too restless. While the patient is under the effects of the anæsthesia it is a wise procedure to give glucose saline per rectum—about a pint for adults—as it is retained and absorbed quickly.

The patient is returned to bed and kept between sterile sheets under an electric cradle if necessary. After a week or even earlier, there won't be any necessity to confine the patient to bed. In the series that came under my care, I had to keep only two cases in bed beyond a week. The others had ambulatory treatment. The coagulum is kept for about three weeks when it peels off easily. No attempt should be made to pull it off forcibly as the adherence means that the surface underneath is not completely healed. The advantages of this method are :—

- (1) The easy application of the treatment and the avoidance of repeated spraying or dressings.
- (2) Comparative comfort to the patient and shortened period of hospitalisation.
- (3) The immediate stopping of loss of fluids and the absorption of toxic products.
- (4) The prevention of infection.
- (5) The simplification of nursing.
- (6) The antiseptic effect of silver nitrate.

No absorption of silver takes place even when large amounts of solution are used as proved by the fact that in none of the cases treated has argyria been seen.

The general treatment adopted is the administration of fluids,

light and nutritious diet and stimulants such as brandy and glucose when indicated. In the stage of secondary shock where the chief danger is due to dehydration intravenous glucose saline or blood transfusion is necessary. In the stage of acute toxæmia there is no indication for giving fluids by the intravenous route except blood transfusion by drip method when there are signs of circulatory failure. As the liver shows changes very early, liberal administration of glucose should be a routine measure. One of the drugs that is very useful in the stage of acute toxæmia is eucortin, and the rationale of giving it can be appreciated if one realises that the suprarenal cortex shows changes in that stage. It is administered in doses of 1 c.c. in the case of children and 2 c.c. in adults. This is repeated at intervals of two to three hours till the patient tides over the critical stage in acute toxæmia.

If there are any signs of septic toxæmia or even as a prophylactic measure, prontosil or sulphanilamide is used as the organism that is responsible is a streptococcus.

I have tried in this paper to bring out the rationale of the modern coagulation treatment of burns which has a close bearing on the pathological processes. The tannic acid silver nitrate treatment is a definite advance in coagulation therapy and its application which can easily be adopted by the general

practitioner will stop or at least mitigate the ravages due to the accident of burns.

I express my grateful thanks to Major J.F. Shepherd, L.M.S., First Surgeon, King George Hospital

for the facilities and encouragement given to me in adopting this treatment.

The following clinical photos illustrate the results of treatment with tannic acid and silver nitrate.

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Diphtheria Prophylaxis.

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Abstract of a paper read before the Medical Association of the King Institute, Guindy, presided over by Lt.-Col. H. E. Shortt, C.I.E., I.M.S.

1. Historical.
2. Products used.
3. Use of Schick Test and the Moloney Test.
4. Mode of administration and the therapeutic value of the prophylactics.
5. Control of Institutional Epidemics.

Historical.

The evolution of our knowledge of Diphtheria is similar to that of many other diseases, the etiology of which is now known with exactness. From a chronological point of view, this knowledge naturally falls into 4 main periods. In the first place, there is that which may appropriately be called the era of clinical observation.

During this, epidemics and cases were noted and described but no certainty could be attained, because dissimilar states were classified as identical merely on the ground of superficial resemblance. A confusion also ensued from the protean characters which the disease assumed in different epidemics or in different individuals. The first was succeeded by the second or pathological—

anatomical period in which a more exact knowledge was possible by virtue of the refined technique of pathological histology. Although numerous records of autopsies are to be found in the literature of the clinical period, it was the development of the microscope and the rise of the Doctrine of Cellular Pathology in the hands of Virchow, which led to a more exact knowledge of the essential morbid changes at work in the production of the Diphtheritic lesions. Bretanneau in 1826 regarded Diphtheria as a specific disease and separated it into a clinical entity from clinical and pathological observations.

Nevertheless, the pathological anatomical period came to an end without the exact determination of the cause of the disease.

A third experimental and etiological period followed. At first attempts were directed to show that Diphtheria can be reproduced in animals experimentally and with the demonstration of this fact the causative agent of the disease was searched for and found by Loeffler in 1884 though in the previous year, Kleb observed the organism in the false membrane and describ-

ed their characters but made no cultivation. Loeffler first isolated the organism in pure culture, from the throats of patients suffering from clinical Diphtheria and thus established the disease as a Bacteriological entity. He gave an account of its cultural characters and its pathogenic effects in animals. Confirmation of his work was soon attained and everywhere a great activity prevailed in the study of the Diphtheria Bacillus and its life history. In 1888, Roux and Yersin made an important discovery that a potent extra cellular toxin can be obtained from the filtrate of a culture of Diphtheria Bacillus. The lesions produced by this toxin were exactly identical with those which followed the injection of the living organism. Thus, it was established that *C. Diphtheria* produced pathogenic lesions through its exotoxin and that there was no spread of the organism beyond the local lesions. In 1890, Von Behring and Kitasato first studied the immunological aspects of *C. Diphtheria* and made their memorable discovery of Diphtheria anti-toxin and initiated the era of serum therapy. They established beyond doubt that a specific anti-toxic serum could be prepared to neutralise its toxin and thus confer immunity against the disease. This constitutes the fourth and the last classical period in our knowledge of the disease. Behring's fundamental discovery was the starting point for numberless investigations, which have added vastly to our scientific knowledge. Innumerable obser-

vations of the clinical value of the treatment by Antitoxin particularly the thorough investigations of Emil Roux have expelled all doubts as to its efficacy. The mortality statistics before and after the introduction of antitoxin have demonstrated the enormous reduction in the death rate in Diphtheria brought about by the use of this remedy. In fact, Behring's discovery conferred an incalculable benefit upon the human race. Like all other important advances in knowledge, the discovery of antitoxin for Diphtheria was not wholly the sudden inspiration of one great man but rather the last stone of an edifice whose foundation had been laid by the great thinkers of the past and whose fabric had been built up little by little by the medical scientists of the 19th century.

No further serious discovery was made after this till the year 1908 when Professor Bela Schick of Vienna succeeded in introducing a specific method, the Schick Test, in diagnosing the susceptibility of persons to Diphtheria infection. On the basis of this specific test was started the active immunisation of susceptible children by a Toxin-Anti-toxin mixture with marked success.

Toxin of *C. Diphtheria*.

Toxin of good flocculating value is essential in the production of potent Diphtheria prophylactics. Good toxin production is influenced by a number of factors which may be summarised as follows:—

- (1) Strain of the organism used.

- (2) pH of the medium.
- (3) Medium used.
- (4) Temperature and time of incubation.
- (5) Care of the strain.
- (6) Manner of inoculation into flasks and nature of flasks used.

Post-Mortem Appearances of Toxic Death in Animals

Local effects.—At the site of inoculation a massive gelatinous and sanguineous oedema is developed; usually there is a varying amount of inflammatory exudate in the form of thin greyish white membrane. The regional lymph nodes are enlarged and congested.

General effects.—The most constant and characteristic lesion is found in the adrenals. Both the organs are enlarged, congested and dark red in colour. On section, extravasation of blood is seen inside the substance of the organ. Sometimes, punctiform hæmorrhages are present. Besides, there is marked congestion of the kidneys, oedema of lungs and effusion into pleural and pericardial cavities and necrotic changes in the heart and liver.

The Schick Reaction.—Was introduced by Bela Schick of Vienna in 1913 to determine the susceptibility of individuals to Diphtheria. It has been observed that the presence of about 1/50 to 1/20 unit of Diphtheria Anti-toxin per c.c. of blood gives immunity to Diphtheria. Such an amount of anti-toxin if present, prevents any reaction after injection of 1/50

M.L.D. of Diphtheria toxin. This amount is often present in normal persons who have acquired it from a preceding infection with C. Diphtheria with or without any accompaniment of the disease. The new born infant obtains it from its mother's blood through the placental circulation and the immunity thus acquired gradually and progressively diminishes after a year, unless it is again supplemented or increased by subminimal infection. Hence, the greatest incidence of the disease is after one year when the inherited immunity almost wears off. This basic level of 1/30th unit of Anti-toxin was first determined on a limited number of children by Michiels and Schick and later confirmed by Kolmer and Moshage. From the experimental data of later investigators, it appears probable that the majority of Schick positive reactions contain less than 1/200th unit of Anti-toxin per c.c. and the majority of Schick negative reactions over 1/25th unit (Fraser and Halpern). But, what the proportion of the negative and positive reactions of those with an anti-toxic content between these values is, it has not been established. Branden and Fraser reported in 1936 that their findings substantiated the fact that the anti-toxin level of Schick immunity lies between 1/500 and 1/250 unit of anti-toxin when the Schick test material conforms to the standard recommended by the League of Nations.

Materials required for the Test :—

1. Standard Diphtheritic toxin of which 0.1 c.c. = 1/50 M. L. D.

2. Control Toxin (Heated toxin).

Technique.

After cleaning the flexor surface of the forearm with alcohol 0.1 c.c. (1/50 M. L. D.) of the standard Diphtheritic toxin is injected intradermally so as to raise a definite bulla. A 1 c.c. tuberculin syringe with a sharp fine needle may be employed for this purpose and after washing it or preferably using another syringe, an equal amount of control toxin (heated toxin) is injected in a similar manner into the opposite forearm.

Results.—Four varieties of reactions are observed.

1. **Negative Reaction.**—This shows that toxin is neutralised by anti-toxin which is present in sufficient amounts in the blood of the individual to render him immune from Diphtheria.

2. **Positive Reaction.**—Indicated by the appearance of a pink halo around the site of the injection and the development of an oedema at the end of 24 to 36 hours. On the 4th day, the swelling becomes maximum. The reaction gradually fades on the 7th day leaving a small amount of brownish pigmentation for weeks. The control injection on the other arm shows no redness or swelling. These persons have not sufficient amount of anti-toxin to neutralise the injected toxin, and hence, they are susceptible to Diphtheria infection.

3. **Pseudo reaction.**—This is evidenced by an area of redness

which is often urticarial and indurated. It appears early (within 6 to 12 hours) and disappears mostly by the 4th day leaving no pigmentation. It occurs equally in both arms. Such a reaction is due to the presence of Bacterial proteins in the toxin. Such an individual is immune to Diphtheria.

4. **Combined reaction.**—Pseudo and positive reaction occurs in both arms:—a pseudo reaction in the control arm, whereas on the test arm, a combination of Pseudo and positive reactions. The reaction indicates that the individual is susceptible to Diphtheria.

In the Boston City Clinic where I had occasion to see a number of these tests performed, great importance is attached to the reading on the 4th day and the 7th day. The pseudo reaction disappears mostly by the 4th day while the positive reactions persist till the 7th day.

Value of the Test

A positive Schick test signifies that the individual is susceptible and requires immunisation. A negative Schick test shows individual immunity. Carriers of virulent C. Diphtheria always give a negative Schick reaction. In this way, Schick reaction provides a means of determining the virulence of an organism isolated from a suspected carrier. If the supposed person gives a positive Schick reaction, it signifies that the organism is a-virulent. In passing, it may be mentioned that in order to obtain a true reading, the test must be carried out with

great accuracy and some slight experience is required for this.

The Quantitative Schick Test.

The Schick test may be performed quantitatively if a series of injections are made with graduated dose of toxin. Intracutaneous injections of a series of doses consisting of 1/50 M. L. D. 1/25th, 1/15th, 1/10th M. L. D. are made. Glenny, Hopkins and Pope presumed that a tolerance to 1/50 M. L. D. (1 Schick dose) corresponded to an Anti-toxin content of 1/250th of a unit. This test may, thus, be regarded as a simple, though rough, method of fixing the anti-toxin level in blood on a single occasion.

Prophylactic Immunisation.

Prophylactic immunisation against Diphtheria naturally falls into two groups—passive and active. However, our present methods of controlling diphtheria as a herd disease depends almost entirely on active immunisation. Passive immunisation has a very restricted application because of its transitory nature; the immunity induced after the use of Diphtheria anti-toxin as a prophylactic does not last for more than 3 weeks.

Since anti-toxin is always associated with the specific serum protein of the animal in which the anti-toxin has been produced (in the case of Diphtheria, it is in the pseudoglobulin), the duration of immunity depends on the rate at which the foreign protein is eliminated. Homologous proteins are eliminated but

slowly; the passive immunity of infants derived through maternal transmission lasts about a year. Heterologous serum is rapidly eliminated and passive immunity acquired by the injection into man of anti-toxin obtained from a horse is lost in about 3 weeks.

It is the opinion of many authorities that susceptible contacts should not have any prophylactic anti-toxin immunisation, but that they should be isolated and carefully observed for the development of clinical signs of Diphtheria. Also, the chances of the patient developing anaphylactic symptoms are very great if ever there arose a necessity to give large doses of anti-toxin consequent on his developing active Diphtheria. As soon as a positive clinical diagnosis is made, anti-toxin should be administered at the earliest moment. The prophylactic injection of anti-toxin should therefore be looked upon as a weapon for use in serious emergencies which are rare and even then as a palliative, because it leaves the state of emergency to develop again in 3 weeks.

Thus the objections to Anti-toxin prophylaxis are:—

1. The duration of protection is short;
2. Renders the subsequent therapeutic injection less effective owing to the development of precipitins in the blood.
3. Risk of anaphylaxis during subsequent serum treatment.
4. Carriers of virulent bacilli are created by this immunisation.

Active Immunisation.

A clear understanding of the principles that govern the application of this method in the control of the disease is important to the physician in general practice as well as to workers in Public Health activities. Observations in various parts of the world on the behaviour of immunised persons when exposed to the risk of natural infection in Diphtheria leave no reasonable doubt that active immunisation, properly performed, is highly effective in protecting the individual against Diphtheria. It may be noted that, in the few instances in which Diphtheria in an immunised person or in a fully immunised community has been recorded, the infection has almost always been of the Gravis type and even then the infection has not been severe.

Before entering into a consideration of the products used to induce active immunity against Diphtheria, it is well to refer to the doctrine of primary and secondary stimuli in regard to immunity response. We are indebted to Glenny and Sudmersen for their masterly study of this phenomenon which is of considerable moment not only in the immunisation of a population but also in the manufacture of potent anti-toxins.

What is Primary Stimulus?

The injection of an antigen into a normal animal is followed not only by the production of antibody but also by increased ability to respond to a subsequent injection. In other words, a

condition of potential immunity is induced in the animal by the first injection which is capable of marked reactivation by a second injection or what is called the secondary stimulus. There is always a latent period between the primary stimulus and the appearance of immunity. This latent period has been estimated to be about 3 weeks and the accelerated production of anti-toxin takes place when the secondary injection is administered after this period. Glenny and Allen showed that even a minute amount of antigen given as secondary stimulus was sufficient to provoke a pronounced secondary immunity response. In one example, quoted by them, a rabbit which has previously received a primary stimulus but had not produced detectable anti-toxin (*i.e.*, less than 1/2000 unit per c.c. of blood) produced 1 unit of anti-toxin per c.c. 7 days after the intracutaneous injection of a Schick dose of Toxin (1/50 M. L. D.).

It is clear how a knowledge of the essential difference between primary and secondary stimulus response is necessary for the successful immunisation of animals or of man. I have seen these principles employed very advantageously in the University of Toronto by Dr. McKinnon, Chief of the Department of Biologicals, in the hyper-immunisation of horses against toxins to which they have no natural anti-toxin such as most of the pathogenic anaerobes (Tetanus, Welchii Dysentery), etc. Dr. McKinnon gives a few injections of toxoid to his tetanus

horses and then rests the horses until potential immunity develops and then gives subsequent injections which are followed by quick secondary response. In this way, the general condition of the animal is preserved by giving only such injections as are of maximum antigenic value. For the immunisation of children, the Bacteriological Committee of the Medical Research Council suggests that the interval between the first and the second injection should be longer than 2 weeks. The French workers allow an interval of 3 weeks to elapse between the first and the second injection. If the interval is sufficiently long to allow potential immunity to develop, then the second injection acts as a secondary stimulus and a rapid production of anti-toxin follows.

Individuals Refractory to Immunisation.

A certain proportion of adults remain non-immune although they have been exposed throughout their life to infection on many occasions. Two alternative explanations offer themselves: either some individuals possess another line of defence against invasion so that they never receive antigenic stimulation of Diphtheria toxin or they give no response to small doses of toxin. It has been found that Schick positive adults are difficult to immunise. Schick has said, "We believe there are individuals who are totally incapable of developing antibodies against Diphtheria". Hiss and Atkinson have shown that the pseudo-globulin content of the blood rises

during immunisation. Ledingham reported that a horse producing an average amount of anti-toxin increased greatly in pseudo-globulin content but another that failed to produce more than half the average amounts had a very high pseudo-globulin content to start with. The latter type of horses are difficult of immunisation. Ledingham's results suggest that the failure of an animal or individual to become immune may be connected in some way with a temporary or permanent condition of their blood. That this condition may be hereditary is suggested by some results recorded by Hirzfeld and Brokman who examined the Schick reactions of 105 children from 42 families. They showed that:—

1. When both parents were Schick positive, all the children were Schick positive;
2. When both parents were Schick negative, most of the children were Schick negative but some young children were positive;
3. When one parent was Schick negative and the other positive children of the same blood group as the Schick positive parent were also positive, while those of the same blood group as the negative parent were mostly negative but a few were positive. It appears probable that the ease of immunisation may be hereditary and transmitted along the same lines as blood-grouping. This was suggested by Theobald Smith as early as 1903 when he stated in reference to transmission of

immunity that "if the father exerts any influence upon his offspring it must be in transmitting a greater lesser capacity for the production of anti-toxin".

Non-Specific Factors in Diphtheria Prophylactics.

The amount of antibodies produced in an animal as a result of injection of a prophylactic depends upon many factors an addition to the degree of immunity already present.

Immunity response may be lessened or repressed by active production of another antibody or by blockade of cells of reticulo-endothelial system or by a general lowering of the health of the animal. Also, it is possible that presentation of an antigen in such a form and such a manner that it can be rapidly eliminated will not result in immunity response, while immunity response to an antigen can be increased by addition of number of non-specific substances such as turpentine, tapioca, alum, etc. Finally, the injection of certain salts, notably manganese chloride may produce an increase in circulating anti-toxin in animals actively immune. Roman studied non-specific stimulating effects of tapioca by injecting horses with anatoxin and tapioca (in the proportion of 100 parts of toxoid plus 1 part of finely powdered and sterilised tapioca) and he found a significant increase in the anti-toxic values of the horses compared with those of his controls which did not receive tapioca. With Tetanus immunisation even greater differences were obtained. There

is considerable evidence to show that injection of a slightly toxic antigen causes a better response than that of antigen entirely free from toxicity. Other toxic substances may also act in the same way. Mason has found that antigenic value of lamb Dysentery Toxoid is considerably increased by the addition of a little of the toxin. In another experiment, the antigenic value of Diphtheria Toxoid was improved by addition of B. Welchii toxin. It is presumed that this may be due to non-specific stimulation of the reticulo-endothelial system by the B. Welchii toxin.

Diphtheria Prophylactics.

Unaltered toxin is of no value for human immunisation because doses that can easily be tolerated by all subjects are too small to have any antigenic value. Toxin has, therefore, to be combined with anti-toxin or rendered non-toxic by chemical or physical means. The following are the chief preparations that are suitable for use:—

1. Formol Toxoid (Ramon's Anatoxin F. T).
2. Park's Toxin-Anti-toxin mixture T. A. M. (1/10 L+ mixture).
3. Toxoid-Anti-toxin mixture.
4. Toxoid-Anti-toxin floccules T. A. F.
5. Alum precipitated toxoid A. P. T.
6. Sodium Ricinoleate toxoid.

Formol Toxoid.

This is modified toxin which has lost its properties while still retaining the original powers of flocculation and antigenic capacity. Glenny and Hopkins first suggested the use of toxoid alone for human immunisation. A few months later Ramon used completely modified toxin and suggested the term anatoxin. The term has not generally been accepted in England and America where the well established term toxoid is preferred. Ramon uses 0.3 to 0.4 per cent. commercial formalin and leaves the toxin for about 1 month in the incubator. Too high a concentration of formaldehyde is not advisable and a longer exposure at lower concentrations preferable. The rate at which a batch of toxin loses its toxicity may be shown by the following figures of Ramon (1924). 0.35 per cent. formalin was added to a toxin and samples examined after incubation for various lengths of time.

Original toxin contained	800 M. L. D.
After exposure for 1 day.	50 "
" " 3 days.	10 "
" " 10 days.	1 "
" " 20 days.	1/4 "
" " 30 days.	0 "

For general routine purpose the rate of toxoiding can be traced most conveniently by means of intracutaneous tests in guinea pigs and measuring the extent of reaction. Mode of function of formaldehyde is not clear. It is possible that modification is brought about by combination of formaldehyde with the free amino group of the toxin solution.

Ramon studied the action of a number of other toxoiding agents whereby the toxin loses its toxicity but retains its flocculating and immunising power and they were acrolein, crotonic aldehyde, acetaldehyde, hexamethylene tetramine etc. But none of these have found the general application accorded to formaldehyde.

Formol toxoid and alum toxoid are highly effective antigens but have a tendency to cause troublesome local and general reactions when administered to older children and adults. This can be predicted in the individual case by a preliminary test originally advocated by Moloney and Fraser (of the Connaught Laboratories, Toronto) and called the 'Moloney Test' in which a minute amount of the toxoid, in question is injected intradermally at the same time as the preliminary Schick test is carried out. The occurrence of a local skin reaction indicates that the individual is sensitive and if so the dosage of the prophylactic should be reduced or an alternative preparation used. Both the toxoid anti-toxin mixture and the toxoid-anti-toxin floccules are much less likely to produce these reactions. Of these T. A. F. is the more effective antigen and should be used in preference to ordinary toxoid in older children and adults specially if a preliminary test with toxoid reveals sensitiveness. In general, the dose of these preparations is 1 c.c. administered on 3 occasions at intervals of 2 to 4 weeks. The resulting immunity could be controlled by a subsequent Schick test

which, should be negative if the prophylaxis has been effective. Immunity is developed in about 4 to 12 weeks and lasts at least about 8 to 10 years. The Therapeutic Substances Act of Great Britain (corresponding to the Regulations of the National Institute of Health, Washington D. C.) prescribes tests which ensure that commercial supplies of Diphtheria Prophylactics shall not be too toxic and at the same time possess efficient immunising properties.

Two questions should be answered before any diphtheria prophylactic is passed as fit for human use:—

1. What tests should be performed to determine the suitability of a lot?
2. What should the tests show in each case?

The suitability of a lot of Diphtheria Toxoid depends upon (i) its atoxicity; (ii) its immunising value. Test for atoxicity: the intradermal test on the guinea pig should be negative and 5 c.c. injected into pig should not produce any local reaction and must produce sufficient anti-toxin to make the animal withstand larger L + doses of toxin.

Alum Toxoid.

Glenny and his co-workers found in 1930 that on account of its rapid elimination, formol toxoid does not produce a continuous stimulus but when it is converted into a relatively insoluble precipitate by treatment

with potash alum even more effective antigenic action is secured. Glenny suggested that this high immunogenic efficiency is probably due to delayed absorption of the precipitated toxoid from the site of inoculation with a consequent prolongation of the antigenic stimulus. The results obtained have awakened hopes that it may be possible to induce an effective immunity with a single inoculation. The administrative advantage of such a method are obvious especially in mass immunisation.

Many published reports indicate that the one shot method may become a routine procedure but other records (particularly of Fraser and Halpern of Toronto who have done a tremendous amount of work on the subject) indicate the wisdom of suspending judgment until we have a far more extensive experience. Parish working in the Wellcome Physiological Laboratories in Beckenham observed in 1936 that the success of one shot immunisation against diphtheria is largely dependant on the basal immunity of a community. Where the natural Schick negative rate is high a single injection of 0.5 c.c. or 1 c.c. of A.P.T. will convert well above 90 per cent. of Schick positive individuals to Schick negative within a few weeks; but where Schick negative rate is low, the two dose method will have to be adopted. A. P. T. sometimes produces unpleasant local reactions and for this reason, it is advisable to do a preliminary Moloney test particularly in

older children and adults before injection of the full dose. Bauxton and Greenwald working in the Bureau of Laboratories, Department of Health, New York City, made a detailed study of A. P. T. in 1935 and found that a toxoid of good flocculation value is needed for this purpose and that 1.5 to 2 per cent. alum concentration was needed for the maximum precipitation of alum toxoid. They also found that if the toxoid did not precipitate by the addition of alum, the addition of solid NaCl brought about the precipitation. A better product was obtained when the toxoid was heated to 40°C prior to precipitation. In children under 3 years, the dose is 1 c.c. repeated again after 3 weeks and then again after 3 weeks. In older children and adults 0.1 c.c. is given as first dose and if no annoying reaction is seen a second injection of 1 c.c. is given. If the Moloney test is positive evidenced by redness, oedema and swelling, the amount of the following dose is 0.2 c.c. Wet dressings of a saturated solution of boric acid are quite helpful in reducing the soreness and swelling. In about 4 per cent. of adults, some temperature and a feeling of malaise may develop. An abscess occurs in an average of 1 in 1000 injections. It heals readily, however.

T. A. F. (Toxoid-Anti-toxin Floc- cules.)

Manufacture:—This product contains all the specific antigen and antibody with relatively little non-specific materials, and the relative absence of non-speci-

fic material makes the floccules particularly useful for human use. On the basis of the flocculation point toxoid and anti-toxin are mixed in equivalent proportions. Flocculation is permitted to occur at room temperature for 24 to 48 hours. The mixture is centrifuged and washed in saline 3 times; then dissolved in distilled water 4 times less than original volume. The floccules are heated to 82°C for 20 minutes to destroy the anti-toxic power of the floccules and to stabilise the products; 1:10000 merthiolate is added as a preservative. Dose 1 c.c. to be injected 3 weeks apart. The resulting concentrated and purified antigen is claimed to possess all the characteristics of a toxoid namely thermo stability, irreversibility, specificity and flocculating and immunising powers. This substance confers quite good immunity and is reputed to give little reaction in adults.

Toxin-Anti-Toxin Mixture.

The use of this mixture has been very generally abandoned.

Control of Institutional Epidemics.

Immediately the first case of Diphtheria occurs in an institution, a Schick test must be performed on all inmates and nasal and throat swabs taken. Children below 8 years need not be Schick tested because very few children below this age are Schick negative. The Schick negative and swab positive subjects should be regarded as carriers and retained in isolation. The Schick negative and the

Diphtheria Prophylaxis

swab negative people are uninfected and immune and can be released from isolation. The Schick positive and the swab positive should be regarded as probably incubating Diphtheria and kept under constant observation and treated with anti-toxin immediately any clinical signs develop. Those who are Schick positive and swab-negative are uninfected but susceptible and so should be immunised.

All cultures or morphologically typical Diphtheria should be tested for virulence. Those Schick negative persons who are carriers of avirulent bacilli may be released from isolation. But, the immunes who are carriers of virulent bacilli and who must be regarded as potential disseminators of infection must be kept under observation until they cease to carry.

The following technique is adopted by Fraser and Halpern in the Connaught Laboratories at Toronto in the performance of the virulence tests:—

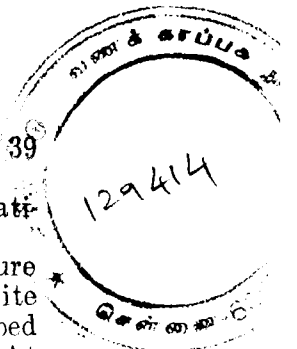
An 18-hour culture in Loeffler's medium is used. 1 c.c. of broth is added to the tube and the

growth is emulsified with a platinum loop.

Inject 0.1 c.c. of the culture intradermally into a white rabbit whose skin has been clipped by an electric hair clipper. At the same time inject in a different place 0.1 c.c. of a known virulent culture with another syringe. This latter forms a check upon the test. In the same syringes keep 0.1 c.c. of the same cultures in the cold room. Five hours hence inject the rabbit intravenously with 500 units of Diphtheria anti-toxin in 2 c.c. saline. After that inject the remaining 0.1 c.c. of the unknown and known cultures that has been kept in the cold. The skin reactions will be very marked and decisive after 48 to 72 hours in the case of virulent cultures given before the intravenous administration of anti-toxin while the reactions after the administration of anti-toxin are practically negligible. If the unknown culture produces no reaction, before and after the injection of anti-toxin, then the conclusion is the culture is avirulent. But the known culture should have produced a marked reaction in the same animal before the injection of anti-toxin.

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Extra Uterine Pregnancy*

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When the fertilised ovum is arrested at any point between the Graffian follicle and the uterine cavity, we designate the condition as ectopic pregnancy. The term ectopic pregnancy originally coined by Robert Barnes is a more widely inclusive term than extra uterine pregnancy. It includes cases in which pregnancy may be ectopic without being extra uterine such as

- (1) an interstitial pregnancy,
- (2) pregnancy in the rudimentary horn of a bicornuate uterus, and
- (3) those rare conditions described by Doderlane and Herzob in which pregnancy occurred in an adenomyomatous uterus.

The prevalence of ectopic pregnancy as compared with intra-uterine pregnancy has been estimated by Schumann as one in two hundred. Farrar found the ratio as compared with other gynaecological conditions to be 1.5 %. According to Wynne it is 1.3 %. Our ratio in the Gosha Hospital for 1939 was 1% and for 1940, 1.1%.

The first mention of this anomalous pregnancy was made by Albucassis the well known Arab surgeon (1013-1106) in his book *Al Tarsif*. In the case described by him gestation sac had suppurated and the abscess perforated through the abdominal wall.

Prior to 1838 ectopic pregnancy was often confused with rupture of the pregnant uterus. The papers published by Velpeau and Dezemiers in 1836 made out the differentiation between the two conditions.

Extra uterine pregnancy has been reported also in the lower animals.

Aetiology.—may be broadly classified under three headings.

- (1) Conditions which interfere mechanically with the downward passage of the ovum;
- (2) Conditions resulting from inflammatory affections in the pelvis which also may cause obstruction; and
- (3) Physical and developmental conditions which favour decidual formation in the tube.

I. Condition which interfere with the downward passage of the ovum mechanically.

(i) Peritoneal adhesions which compress the lumen of the tube or adhesions which bind down the tube and restrain its movements.

(ii) Myomata and other tumours which press on the tube. In one of our cases done in January 1941, there was a small nodule at the uterine end of the tube which might have been the

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cause of tubal pregnancy. The tumour on microscopic examination was found to be an endometrioma of the fallopian tube.

(iii) Tubal Polypi—a comparatively infrequent cause.

(iv) Persistence of the foetal convolutions of the tube in later life.

(v) Excessively long tube.

(vi) Inflammation of the ovum in a diverticulum of the tube. These diverticula usually end blindly and so the ovum gets arrested.

(vii) Accessory ostia also act very much like diverticula.

(viii) Spasm of the tube, muscle insufficiency and antiperistalsis.

(ix) Tortion of the tube.

(x) Endometriosis of the tube or ovary or cul-de-sac.

(xi) External migration of the fertilised ovum has been proved in a number of cases. Such a phenomenon may favour the production of extra uterine pregnancy, since the fertilised ovum may attain such proportions during its migration as to prevent its passage through the tube and get arrested. Preservation of the zona radiata during the time the fertilised ovum is in the tube prevents its implantation; if due to some delay the zona radiata has disappeared before reaching the uterine cavity, the trophoblast burrows into the tissues of the tube.

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(xii) Increased invasiveness of the trophoblast covering the ovum, favouring ready nidation has been attributed as a cause of ectopic pregnancy and this might be due to deformation.

(xiii) Abnormal corpus leuteum is said to be a cause of ovarian pregnancy.

Conservative gynaecological operations performed for the relief of sterility may be a predisposing factor for subsequent development of extra uterine pregnancy.

II. Conditions resulting from inflammatory affections.—Salpingitis may act either by the loss of cilia which should favour the motion of the ovum to the uterus or by gluing the folds of the mucosa of the tube together and by forming blind pouches in which the ovum is caught or by occluding the tube through swelling or kinking or by paralysing tubal contractions. Gonorrhœa is a frequent antecedent, and appendicitis also may cause it.

III. Physical and developmental conditions which favour decidual formations in the tube.—Webster believed that tubal pregnancy occurs if the tubes are capable of decidual reaction which he considers represents a reversion to an earlier type and therefore should be regarded as a sign of degeneracy. But in many instances the condition has been noted in fully developed women living in the best of surroundings. Moreover its great rarity in the lower animals also is against such a view.

* Paper read before the Gynaecological and Obstetrical Society, Madras.

Anomalies of the fertilised ovum are also said to be a cause of ectopic pregnancy but the abnormal development of the ovum may be the result of implantation of the ovum in unsuitable environment resulting in defective nutrition.

A very rare cause of ectopic pregnancy is post operative separation of the edges of the uterine wound of a previous caesarean section. Four cases of this kind in which primary abdominal pregnancy occurred are recorded by E.L. King in 1932. In three of these the ovum had implanted itself on the omentum which filled the gap between the ununited uterine edges while in the fourth case the ovum was implanted on the peritoneum of the anterior abdominal wall.

Classification.—A natural classification of the various forms of ectopic pregnancy is one based on the original point of implantation of the fertilised ovum; when it remains and develops where it was first arrested we designate it as *primary* ectopic pregnancy and upon changing its position by rupture or further development it is called *secondary* ectopic pregnancy.

I. Primary tubal forms—according to their site are as follows:—

(1) Interstitial which may become intra-uterine.

(2) Isthmial.

(3) Ampullary.

(4) Infundibular which may become secondarily tubo-ovarian or tubo-abdominal.

Other secondary forms are (1) secondary abdominal; (2) intra-ligamentary which may become a mileary abdominal pregnancy.

The term tubo ovarian pregnancy is used when the foetal sac is composed partly of tubal and partly of ovarian tissue. Such cases owe their origin to the development of an ovum in a tubo-ovarian cyst or in a tube whose fimbriated extremity was adherent to the ovary at the time of fertilisation.

II. Ovarian pregnancy which may become abdominal or ovario-abdominal.

III. Primary abdominal.

IV. Pregnancy in a rudimentary horn.

Of the primary tubal forms ampullary is the commonest, then the isthmial and lastly interstitial which is the rarest of all; we had one in our series.

Criteria of an interstitial pregnancy.—This form is distinguished from the commoner forms by the position of the round ligaments on the outer side of the sac where the uterine tube also is found. The uterus is enlarged and is intimately connected with the inner side of the tumour of which it appears to form an organic part. The tubo-ovarian mass may bulge into the uterine cavity and be separated from it by a small opening or may be freely connected with it, when the foetus escapes into the uterus, the placenta stays behind in the wall and communicates

with the uterine cavity through the small opening.

An interstitial pregnancy is liable to be confused with pregnancy in a rudimentary horn in which also the round ligament is found on the outside of the sac. This error will not occur if the uterine body is noted rounded off towards the rudimentary side and the attachment of the pedicle of the tumour low down on the side of the uterus is observed. The uterine tube is also inserted lower down on the side of the tumour, that it is on the other side. An interstitial pregnancy may also become intra-ligamentary.

Of the secondary forms intra-ligamentary form is some times difficult to distinguish from a ruptured intraperitoneal form encapsulated in adhesions. The following are the criteria of differentiation. The tumour occupies the same relations to the broad ligament and the uterus as does an intra-ligamentary cyst; the meso-salpinx is unfolded together with the anterior and posterior layers of this broad ligament and the pelvic peritoneum and even the peritoneum of the anterior abdominal wall has become detached from the cellular tissue and covers the tumour according as the pregnancy is more or less advanced. The ovary lies some where upon the surface of the tumours flattened or drawn out as the case may be but the ovarian tissue is not distributed over any considerable area, thus affording a differentiation from ovarian pregnancy.

The uterus lies closely applied to the tumour, deprived of its broad ligament on the side of pregnancy and is pushed over to the opposite side. The round ligament extends from the corner of the uterus over the front of the tumour which lies also in intimate relation with the upper half of the vagina. Muscular tissue is often found abundantly on the sac wall derived from the tube and from the subserous tissue.

Ovarian Pregnancy.—Upto 1878 there did not exist any criteria by which ovarian pregnancy could be judged. In that year Spiegelberg reported what he believed to be a conclusive case and formulated his criteria. Twenty years latter in 1898 Catherine Van Tussenbroeck presented at the congress of Medicine at Amsterdam a case in which the ovum developed in the graffian follicle. Since then many more cases have been accepted as ovarian pregnancy and De Lee in his latest edition speaks of 85 cases on record. The Egyptian gynaecologist Mahfrez in his series of 120 cases reports 3 cases which fulfil Spiegelberg's criteria but he thinks only one was primarily ovarian.

Spiegelberg's criteria.—(1) The tube is intact and has no organic connection with the gestation sac.

(2) The tumour is connected with the uterus by the utero-ovarian ligament and the foetal sac occupies the position of the ovary and there should be no separate ovary on the affected side.

(3) The wall of the sac contains graffian follicles in various places.

(4) The tunica albuginea of the ovary passes directly into the tumour wall. The ovary can accommodate itself more readily than the tube to the growing pregnancy. In ovarian pregnancy the ovum itself and its mode of implantation do not differ greatly from that observed in the uterus except that a definite decidua is lacking, so that the formative ectoderm invades the ovarian tissue directly. Most cases terminated by early rupture and intraperitoneal hæmorrhage but patients who have reached full term have been recorded in the literature.

Primary abdominal pregnancy.—Though theoretically possible is doubted by most authors. Occasionally a fertilised ovum may become implanted upon the fimbria ovarica. Such a condition might closely resemble a primary abdominal pregnancy in as much as the surface upon which the ovum was primarily implanted is so small that the margin of the placenta soon extends beyond it and becomes attached to the surrounding organs, thus giving the impression that the peritoneum was the primary site of implantation. A careful microscopic examination enables one to differentiate between the two conditions.

Relative incidence of the various types of ectopic pregnancy.—Interstitial is the rarest. The first case of interstitial pregnancy

was found by Traubar on autopsy. In 1893 he discovered another interstitial pregnancy in a uterus he removed by subtotal hysterectomy. In the same week Lawson Tait described another case which he discovered un-ruptured while operating on a patient supposed to be suffering from suppurating cyst of the ovary. In Mahfrez series of 120 cases there were four cases of ruptured interstitial pregnancy. This is supposed to occur at a later date because there is a dense mass of muscular tissue intervening between the ovum and the peritoneal cavity. The diagnosis of these cases is very difficult because the patient's symptoms are so trifling and severe intraperitoneal hæmorrhage may occur without any warning.

Various terminations of ectopic pregnancy.—The ability of the tube to accommodate the foetus to term is doubted by many authors. Out of the 16 cases collected from the literature by F. Jayle and Dilherm in 1900 in which pregnancy was claimed to have advanced beyond the 5th month, very few were accepted as proved examples. Mahfrez says that he has three specimens in his museum which fulfil the most rigid criteria. Conaway in 1913 reported a case of a dead foetus 6½ lbs. found in an unruptured tube.

(2) Early death of the ovum with complete resorption and restoration of the tube to its pre-pregnant condition. In taking detailed histories of gynaecological cases, it may be possible to elicit a train of symptoms

strongly suggestive of extra-uterine pregnancy at some period of a woman's life. Upon subsequent laparotomy, no evidence of any lesion may be found or a nodular area of fibrosis may exist in the tube suggesting a previous tubal pregnancy.

(3) Death of the embryo with formation of a tubal mole. A tubal mole results when the foetus dies in the intact tube with marked hæmorrhage about it and between its membranes. The liquor amnii is absorbed, the blood gets organised and we get a mole resembling uterine mole.

(4) Tubal abortion either complete or incomplete. There is at first intra-tubal rupture of the capsular membrane of the ovum. According to many authors this termination is the general rule, spontaneous rupture (extra tubal) occurring only in those cases in which occlusion of the abdominal end of the tube prevents the possibility of an abortion. Abortion is common in ampullary pregnancy.

(5) Rupture of the Pregnant tube:—Intraperitoneal rupture and hæmatocele formation. Rupture is the most usual mode of termination according to some authors, while others think that tubal abortion is the commonest. Statistics by different authors vary widely. Schumann says that rupture occurs with twice the frequency of abortion. Mall is of opinion that rupture occurs more commonly when the embryo is normal, than when it is abnormal.

(6) Intraligamentary rupture:—Occurs when the rupture is along the inferior aspect of the tube resulting in broad ligament hæmatoma or it may go on as a broad ligament pregnancy or a secondary rupture occurs into the peritoneal cavity and the pregnancy may go on as a tertiary abdominal pregnancy. Intraligamentary rupture is more common in isthmial pregnancy. If the placenta remains attached to the tube on the side opposite the point of rupture, it generally becomes displaced upward as pregnancy advances and comes to be above the foetus. But when it is situated near the point of rupture, it gradually extends down between the folds of the broad ligament being implanted partly upon the tube and partly upon the pelvic connective tissue. Rupture into the broad ligament is comparatively rare. Mummification, calcification, lithopedion and adipocere formation are some of the rarer sequelæ. Pyogenic bacteria may gain access to the gestation sac and give rise to supuration. If the patient does not die of septicæmia, portions of the foetus may be extruded through the abdominal wall, bladder, or intestines. This is more common in broad ligament pregnancies, due to the proximity of the intestines.

Diseases of the Extrauterine ovum.—The extrauterine ovum is liable to all the diseases of the intrauterine ovum.

(1) Hæmatoma mole has already been mentioned.

(2) Hydatidiform moles have been recorded.

(3) Cases of Chorion epithelioma have been collected from the literature. Resel in 1905 recorded 10 cases.

(4) It is interesting to note that Spiegelberg and Holst observed the occurrence of eclampsia during the false labours of advanced extra uterine pregnancy.

Bilateral tubal pregnancies.—82 cases of bilateral tubal pregnancies have been recorded in the literature upto 1914 but only 33 of these are accepted as genuine cases. In Mahfrez series of 120 cases it occurred only once.

Parkes reported a case of triplets in a patient he operated upon for intraperitoneal rupture of a pregnant tube. At the operation he discovered an unruptured tubal pregnancy on the opposite side. Four days later the patient aborted a six weeks intrauterine pregnancy and so it was a case of combined intra and extra uterine pregnancy. The first case of combined pregnancy seems to have been recorded by Duverney in 1708. Gemel collected 213 cases in 1933. Munro Kerr has described a case of combined ovarian and uterine pregnancy.

Repeated tubal pregnancies.—Primrose in 1594 was the first to describe such a condition. Smith states that patients who had tubal pregnancy once are less fertile than normal but are exposed to a greatly increased probability to ectopic gestation. Thus within 5 years after primary operation 80 pregnancies occurred in his 144 patients in

whom subsequent pregnancy was theoretically possible. Of these 23 cases were reported to be tubal pregnancies. One of our patients operated upon for ectopic pregnancy in May 1939, came this month with a tubal pregnancy on the opposite side.

Effects of extra uterine pregnancy upon subsequent child bearing.—(Williams). The presence of the products of an old extra uterine gestation occasionally gives rise to dystocia and necessitates operative interference. Cases where caesarean section, induction of premature labour and craniotomy had to be performed are recorded in the literature. As a rule however dystocia is not encountered.

Unusual sites of Tubal Pregnancy.—Tubal pregnancy in the stumps of a resected tube occurred in 11 cases in Auvrays' collection in 1923. Four cases of tubal gestation in the sac of an inguinal hernia have been collected by Birmann in 1922.

Signs and symptoms of ectopic pregnancy.—The diagnosis of an ectopic pregnancy is most difficult at times. The classical cases of tubal rupture and abortion are not difficult to diagnose but unfortunately the manifestations of an unruptured ectopic gestation are not characteristic and the patient and her doctor are frequently unaware of the existence of any abnormality until death of the foetus, tubal rupture or tubal abortion occurs. The history of the case usually shows a long period of sterility and close investigation reveals

the existence of previous catarrhal process in the pelvis.

The diagnosis of an intact tubal pregnancy is rarely made, because patients who do not have unusual symptoms seldom visit a physician early enough and secondly it is difficult to be certain of such a diagnosis. Previous to primary rupture, symptoms are practically those of an early pregnancy. The patient misses a menstrual period, there is some nausea and perhaps has slight tenderness of the breast. Pain is not always present. There may be some soreness in the pelvis either general or localised to one side but this is rarely troublesome enough to arouse suspicion of any abnormality for soreness in the pelvis is not uncommon in normal pregnancy owing to the marked congestion of the enlarging uterus. Pelvic examination at this stage shows some tenderness about the adnexa of one side and perhaps a small mass due to the enlarged tube. This may be mistaken for a congested ovary or it may be due to previous inflammatory disease in the pelvis; unless a previous examination has shown the pelvis to be clear making it certain that the little mass is of recent origin, the diagnosis of tubal gestation is hardly justifiable and very often erroneous. An Aschheim Zondek or Friedman's test is of assistance because a positive result is obtained in the early weeks. It seems probable that a large majority of cases set forth as "diagnosed and operated upon before rupture," are really not seen until after the primary

intratubal rupture. The very slight hæmorrhage, the few sharp pains and the marked tenderness are really evidences of primary rupture.

So ectopic pregnancy may be clinically divided into four groups excluding the cases of real unruptured tubal pregnancies.

(1) The fulminant type (rare).

(2) The type of case where the woman suffers for sometime from abdominal uneasiness, pain, occasional faintings and irregular vaginal bleeding. This is the general type.

(3) The case where the woman suffers from pelvic hæmatocele (fairly common).

(4) The rare case where the woman goes to the later weeks of pregnancy.

The fulminant type.—This is seen in its typical form in isthmial pregnancy when rupture occurs. There may or may not be a history of missed menstrual period, depending on the age of the gestation. There may be no premonitory attacks of abdominal pain or vaginal discharge. The woman is suddenly seized with acute abdominal pain of a stabbing nature and has the feeling of something having given way. She faints and collapses, and is blanched, the extremities are cold, with subnormal temperature and cold sweats. The pulse is rapid and thready, respiration is hurried, air hunger and restlessness set in. The abdomen is tender and may have a certain amount of fullness. A bimanual examination

shows extreme tenderness in the fornices, there may be no fullness. Later on, when the blood coagulates it may be possible to feel a soft boggy swelling in the fornices. The condition may simulate a fulminant appendicitis, perforation of a gastric or duodenal ulcer, torsion of an ovarian cyst or any other organ in the abdomen.

The second type is the commonest. The patient suffers for some time from abdominal pain or uneasiness, has occasional attacks of fainting and bleeding from vagina. The pain may be of a colicky character due to the tubal contractions; there may be history of amenorrhoea and subjective symptoms of pregnancy. Bladder irritability, dysuria, and rectal tenesmus may be present. A certain amount of anaemia or even jaundice may set in. On bimanual examination a soft tender pulsating elastic swelling is felt in one of the fornices. The consistency of the swelling and pulsations are not always reliable. The passage of decidual cast may help the diagnosis. This condition may be mistaken for an inflammatory condition of the adnexa or even for a pelvic abscess or it may simulate a retroverted gravid uterus or a uterine abortion.

The third type is when the patient comes with a pelvic hæmatocele. The coagula in the pelvis become walled off by adhesions, the uterus and adnexa or even the intestines may become involved in the adhesions; with the absorption of some of the fluid elements, the pelvic mass

assumes a doughy consistency which does not easily pit on pressure. The patient complains of chronic dull aching pains in the pelvis, with increasing difficulty in micturition and defecation, vomiting, loss of appetite and general malaise. At times the hæmatocele becomes infected and we get all the signs and symptoms of pelvic abscess.

The fourth type is an advanced extra uterine pregnancy. When the extra uterine pregnancy is advanced, the difficulty is not about diagnosing a pregnancy but the question is whether it is an extra- or intra-uterine gestation. In a case operated upon in January 1941 in the Gosha Hospital the condition was diagnosed as pregnancy complicated by an ovarian cyst. The history if elicited may be suggestive. The patient in the early weeks may have experienced symptoms suggestive of a primary rupture. The foetal parts are palpated very easily and foetal movements are easily felt. As the pregnancy advances, the patient may complain of a certain amount of uneasiness or pain in the abdomen, malaise of varying degree, slight fever or even marked elevation of temperature as in our case, due to the toxic absorption. A certain amount of anaemia or even jaundice may be present. X-ray examination may show that the foetus is away from the pelvis or may show foetal abnormalities which are common in an ectopic foetus. On palpation the foetus may be felt on one side. The gravid uterus can be pulled over to the middle line, while the ectopic sac is generally more fixed.

Our case though it was diagnosed as a case of ovarian cyst associated with pregnancy, one noticed that the mobility was far less than one could expect in an ovarian cyst.

On bimanual examination, the cervix may not be soft enough for pregnancy and it may be slightly displaced to one side. It may not be easy to distinguish the uterus as a separate mass.

Later on spurious labour with expulsion of the uterine decidua with a hæmorrhagic vaginal discharge may occur with even evidence of foetal distress; with the death of the foetus the abdominal mass may become smaller and the patient may show symptoms of toxic absorption.

Differential diagnosis :—Conditions that simulate tubal pregnancy, may be grouped into two classes.

I. Those in which the principal feature is a tender pelvic mass associated with some of the other symptoms of pregnancy.

II. Those conditions in which the principal feature is sudden abdominal pain and collapse without apparent cause.

(1) Acute salpingitis may at times simulate tubal pregnancy. Salpingitis is more often bilateral.

(2) Gonorrheal pyosalpinx.

(3) Uterine abortion may be mistaken for extrauterine gestation.

(4) An intra uterine angular pregnancy may be confused with

extra uterine pregnancy. The pregnancy is situated in one horn of the uterus and distends this side, the rest remaining hard. Angular pregnancy cannot be differentiated from interstitial pregnancy before rupture and so the patient should be carefully watched, preferably in a hospital.

(5) A retroverted gravid uterus has to be differentiated from pelvic hæmatocele.

(6) Acute appendicitis is liable to be mistaken for ectopic pregnancy especially if there is a coexisting uterine gestation.

(7) Crosson mentions a rare condition called fulminating pelvic oedema that comes on suddenly without apparent or adequate cause. The sudden onset, the severity of the symptoms and the marked collapse may suggest ruptured ectopic pregnancy. Most of the recorded cases have been associated with chronic inflammatory conditions in the pelvis but the cause of the sudden onset and the exact aetiology is not understood.

(8) A small ovarian cyst especially if coexistent with uterine abortion.

(9) Torsion of an ovarian cyst.

(10) Torsion of the tube.

(11) Rupture of a pyosalpinx may all closely simulate an extra-uterine pregnancy.

(12) Ovarian hæmorrhage. Schröder states that rupture of a graafian follicle may in exceptional cases be followed by profuse

hæmorrhage; that it can prove fatal or cause peritonitis which may terminate fatally or produce an encapsulated blood clot in the peritoneal cavity. Ovarian hæmorrhage when it takes place into the stroma is usually due to pre-existing oophoritis or peri-oophoritis. Other causes of tubal hæmorrhage besides tubal gestation are due to polypi in the tube or inflammation.

(13) Appendicular colic.

(14) Biliary colic.

(15) Renal colic.

(16) Perforation in the gastrointestinal tract may simulate a ruptured ectopic gestation.

(17) Dr. Mudaliar has reported a case of twisted spleen which was diagnosed as ruptured ectopic pregnancy.

Treatment of ectopic gestation.—Lawson Tait in 1883 was the first to treat a case of ectopic pregnancy by deliberately opening the abdomen to remove a pregnant tube although Stephen Rogers in 1867 suggested the rationale of such a procedure. Prior to that time treatment was aimed at destroying the life of the foetus and thus terminating pregnancy without operation, by injecting poisonous substances into the gestation sac or by means of the electric current. The beneficial result of operative treatment was clearly demonstrated by Schauta who after a careful study of the literature in 1891 found that 123 cases were operated upon and 121 cases were treated without operation and

the mortality was 5.7% in the operated series and 86.9% in the non-operated series. At present abdominal section is advocated in almost all cases of ectopic gestation as soon as diagnosed, with very few exceptions. In Gosha Hospital we operate on all cases after diagnosis.

In the rare cases where the unruptured ectopic pregnancy is diagnosed the treatment is abdominal section and removal of the pregnant tube. Blairbell and Whitehouse proposed a more conservative method in these cases. The alternative suggested to salpingectomy was salpingotomy with enucleation. The chief objection to this method is the chance of repetition of the tubal pregnancy. Smith gives recurrence as 3.6%. As regards the other tube it is not necessary to remove it to prevent a possible ectopic pregnancy on that side. Remove the other tube only if it is grossly diseased.

In cases of rupture or tubal abortion with diffuse hæmorrhage, the pregnant tube should be immediately removed. Many of these patients are badly shocked and collapsed and yet from experience we learn that most of these cases could be saved by immediate operation and subsequent treatment of shock and collapse. No time should be wasted in unnecessary exploration and peritoneal toilet. Blood transfusion is helpful if available. We give blood from the peritoneal cavity mixed with 2% citrate solution during the operation.

When the symptoms are less alarming also, it is better to

operate at once as soon as diagnosis is made; waiting overnight may start a fatal hæmorrhage.

Treatment of chronic cases with pelvic hæmatocoele.—Large hæmatocoeles should always be removed abdominally and the sooner this is done, the better it is. Small hæmatocoeles may get absorbed under expectant treatment. Fehling treated 91 cases conservatively with success (De Lee). In such cases the patient should remain on bed until absorption is completed and this may take months sometimes. If the hæmatoma becomes large instead of diminishing in size, interference is necessary. The ovum might be alive and fresh attacks of hæmorrhage may take place. Old standing hæmatocoeles may result in pelvic abscess or cause considerable adhesions in the pelvis with varying degrees of pelvic invalidism and functional incapacity. Our practice is to operate on all these cases when diagnosed; if the hæmatocoele is infected vaginal drainage may be resorted to. Otherwise it is better always to deal with the hæmatocoele by the abdominal route.

Treatment of advanced Ectopic pregnancy:—The consensus of opinion is in favour of early operation irrespective of the fact whether the foetus is alive or dead. A living placenta is more liable to profuse hæmorrhage. Fairbairn pointed out that it was the situation of the placenta far more than the activity of the circulation which determined the amount of

hæmorrhage. Though immediate operation is the accepted practice, in exceptional cases when the child has nearly attained viability and the patient is anxious for a child, the operation may be delayed for a few weeks. But the patient should be in a hospital so that if signs of rupture of the sac occur, immediate operation could be done. The operation can be most difficult at times because of the extensive hæmorrhage and possible injuries to the intestines, ureter etc., when the placenta is attached to the rectum, the sigmoid, small intestines or omentum and further, in the presence of extensive hæmorrhage a complete operation may not be possible. A method advocated is to open the sac at a place with few blood vessels, take out the baby, tie and cut the cord close to its insertion on the placenta, anchor the sac near the abdominal incision and pack the cavity with sterile gauze. The placenta may be absorbed, or it may liquefy producing a fluctuating tumour or it may suppurate. This method entails prolonged convalescence.

Occasionally partial separation of the placenta gives rise to such profuse hæmorrhage that the placenta must be removed at any cost to avert immediate death. One skilled in abdominal surgery alone could tackle such cases.

In the case of pregnancy in a uterine horn, the uterus may be conserved, removing only the pregnant horn; if the main uterine cavity is badly destroyed hysterectomy may be indicated.

Mortality in different series of operations for ectopic pregnancy varies from two to seven per cent. In Mahfrez series it was less than 2%. In the Gosha Hospital the mortality for 12 years from 1929-1940 was 4.5%. Number of cases of ectopic pregnancy from 1929-1940 in the Victoria Gosha Hospital is 67 as shown in the following table:—

1929	1 case	Cured
1930	3 cases	"
1931	1 case	died
1932	1 "	cured
1933	6 cases	"
1934	6 "	"
1935	nil	"
1936	5 cases	cured
1937	6 "	"
1938	2 "	"
1939	16 "	15 " 1 died
1940	20 "	19 " 1 "
	67 cases	3 deaths

4.5 % Mortality.

Ratio of ectopic pregnancy to other gynaecological condition (Gosha Hospital).

1940-1%
 Farran gives the ratio as 1.5%
 Wynne gives the ratio as 1.3%

Analysis of cases 1939-1940. (Gosha Hospital)

Interstitial pregnancy.	1
Isthmial	4
Ampullary	14
Undetermined	17
	36
	—
Intraperitoneal rupture	16 cases
Tubal abortions	10 "
Intraligamentary rupture	2 "
'Unruptured.' (Intra tubal rupture)	3 "
Undetermined termination	5 "
	36
	—

Analysis of cases (Mahfrez)
 Ampullary and Isthmial 96 cases
 Interstitial 4 "
 Tube-ovarian 3 "

Tubo-ligamentary	6 cases
Tubo-abdominal (Secondary abdominal)	4 "
Ovarian	1 "
Primary abdominal	1 "
In a rudimentary uterine horn	5 "
	120 cases

Various terminations	Mahfrez	Polak
1. Unruptured	10	12%
2. Intratubal rupture with partial or complete expulsion of the ovum	27	64%
3. Intraperitoneal rupture	58%	6%
4. Rupture into Broad ligament	5	14%
5. Undetermined termination	Nil	4%

Age incidence of cases from 1929-40 (Gosha Hospital)

From 18-20 years	3 cases
" 21-25 years	25 "
" 26-30 years	9 "
" 31-35 years	19 cases
Over 35 years	5 "
4 cases age not known.	4 "
	65 cases

Periods of sterility for 36 cases (1939-1940)

Absolute sterility	6 cases
Date of birth of last child between 5 and 12 years	9 "
Date of birth of last child between 3 and 5 years	6 "
Date of birth of last child over 18 years	1 case
Date of birth of last child one and a half years in	2 cases

Short notes on Cases: One patient had 3 children and last child was 12 years old and she had 19 abortions and the 23rd pregnancy was tubal pregnancy with isthmial rupture. This patient was sterilised. She passed a complete mtrine decidua 4 days after the operation. Another patient aged 42 years had 10 children and 5 abortions and her 16th was a tubal pregnancy.

Extra Uterine Pregnancy

Another patient a Chinese lady aged 24 years was married for 3 years, had no children or abortions. She had a D and C done in April 1940 and in August she came with two months amenorrhœa and bleeding. She turned out to be case of tubal abortion.

In two cases the first pregnancy was tubal and occurred within one year of marriage.

We had only one case of advanced ~~extrauterine~~ pregnancy. A primipara 32 years old was admitted to the antenatal wards on 3-1-1941 with a history of six months amenorrhœa. She was married at the age of 14 years and had no previous pregnancies. On examination uterus was 24 weeks size with transverse lie of the foetus and foetal heart was audible. There was a bulge on to right side of the abdomen about the level of the umbilicus. P. V. Cervix fairly soft, drawn up. An ovarian cyst of the size of a small unshelled coconut on the right side.

The case was diagnosed as ovarian cyst complicating pregnancy, but one noticed that the tumour was not quite mobile like an ordinary ovarian cyst. X-ray examination showed a foetus and a vague shadow on the left side of the abdomen. Patient since admission complained of pain in the abdomen. Her temperature was 100 98-Pulse 80. Her B.P. was 80 Hb 45% Wasserman-Negative.

Patient was treated with injections of calcium gluconate, hepatox and was given iron by mouth.

She was posted for operation on 15-1-41 but from the 14th she started running a high temperature ranging from 101° to 104° Her urine showed pus cells on microscopic examination and she was given 3 pylopurin injections.

On the 26th her pulse was rather feeble and the high temperature still continued and she was put on digitalin and camphor-in-oil injections. On the 23rd night patient became very ill temperature went up to 103.5°, pulse rapid and thready and abdomen distended—soap and water enema was given with poor result.

The next morning patient was operated on, her pulse was rather feeble. Abdomen was opened by a right para median incision from umbilicus to symphysis pubis. On opening into the peritoneal cavity a small quantity of sero-purulent fluid escaped. The parietal peritoneum was stained with greenish flakes of lymph due to meconium. On exploration uterus was found to be slightly larger than normal and it was attached to the lower and right corner of a purplish tumour arising from the left side of the pelvis. On further inspection the condition was diagnosed as a left broad ligament pregnancy and there was a large purplish bulge on the right side above the main tumour. On this bulge were seen large dilated vessels covered by a thin membrane. On attempting to lift this portion there was a fair amount of bleeding. This was identified as the placenta. The transverse colon was attached to the posterior layer of the

broad ligament, pelvic colon was found to be pushed to the extreme left. Round ligament was stretched over the anterior aspect of the tumour. The finger was introduced between the uterus and tumour, the broad ligament above the uterus was through in segments. Next the finger was introduced between the anterior layer of the broad ligament and gestation sac and separation continued round the anterior end to the posterior side above the attachment of the colon. On trying to lift up the gestation sac, the amniotic sac burst and the foetus began to bulge through the sac. The child was breathing, the cord was clamped and cut. As the two layers of the broad ligament were already split up the placenta with the sac came out easily. The placenta had no adhesions to any organs. The cavity in the broad ligament had some oozing and this was stopped by packing

with hot sponges. A drainage tube was introduced into the cavity in the broad ligament and another into the pouch of Douglas. The two layers of the broad ligament were stitched together and the abdomen was closed in layers.

As the patient's condition was bad to start with, submammary saline was given from the beginning of the operation and during the operation 1½ pints of gum saline was given intravenously. But the patient died about an hour after operation.

The child was slightly asphyxiated but was brought round easily. It had a deep depression over the right mandible and right side of the neck. The child weighed 3 lbs. and lived for 15 hours. The placenta weighed one pound and showed no abnormalities.

Abstracts from Current Medical Literature.

Toxicity of Potassium Salts (*B.M.J.* 1940 ii p. 89 Ed.). The depressant action of potassium has been known to physiologists for over a hundred years, and yet this knowledge has had so little influence on therapeutics. The probable explanation is that the action on the heart is usually symptomless and the first clinical evidence of damage may be sudden death. In a more detailed account of the administration of potassium salts to human subjects in high dosage, Thompson (Q.J.M. 1939: 8: 361) reports that electrocardiograms reveal heightening of the T wave, prolongation of the P-R. interval, heart block and actual cardiac asystole. The changes are similar to those produced by asphyxia and by vagal stimulation. Potassium salts play a part in the chemical transmission of nerve impulses and the morbid effect on the heart may well be due to potentiation of the action of the vagus. In perfectly healthy subjects potassium taken by mouth is excreted too rapidly for these effects to be manifested. Thompson's results were obtained in patients with cardiovascular and degenerative diseases who were treated with potassium citrate or chloride in amounts not exceeding 15 gms. (225 grs.) a day. It is of course to such patients that potassium is commonly given, and Thompson wisely recommends that potassium salts should be

used with the utmost caution in patients with cardiovascular or renal disease. He hints that the administration of mixtures containing anything from 4 gms. of potassium citrate three or four times a day to elderly men with enlargement of the prostate, both before and after operation, may explain why some of these patients occasionally die suddenly. He also suggests care in administering digitalis and potassium simultaneously, as the two drugs may act synergically on the heart.

In a study of the serum electrolytes made at the same time as these electrocardiographic observations, de Wesselow and Thompson discovered that the serum of patients suffering from essential and malignant hypertension tends to show a lower level of potassium than that of patients with a normal blood pressure on the same diet. This is especially marked in malignant hypertension, where low levels of serum sodium also are not infrequent. The significance of these events is quite obscure, and no every striking changes in the blood pressure are brought about by variations in the sodium or potassium content of the diet.

The toxic action of potassium has been approached from an entirely different point of view by workers in America. Bergman and Brury (*J. Clin. Invest.* 1939.

18 : 777) studied the survival time of rats whose kidneys had been completely excised. They found that potassium was toxic and that meat feeding was also harmful, part of this action being attributable to the potassium in the meat. The urine of meat fed rats was highly toxic to the nephrectomised animals, and the chief poison in it was potassium. As a result of various experiments in which the rats were treated with different extracts of meat and with solutions of potassium salts the conclusion was drawn that potassium must be responsible for the high mortality when meat extracts or the alcohol insoluble fraction of meat, was administered, and it is probable that potassium was also a factor in the relatively high death rate observed after the consumption of large amounts of beef. There are therefore good grounds for the orthodox practice of forbidding red meat and prescribing a lacto-vegetarian diet in nephritis. We must again emphasise that medicines containing potassium salts are to be avoided when there is any suspicion of renal insufficiency or cardiovascular disease.

Charcot-Leyden Crystals: (*Lancet*, 1941, January 25th, page 117). Cruschmann's spirals and Charcot-Leyden crystals are known to every one who has read about asthma and though the spirals are probably the casts of the smaller bronchi the significance and nature of the crystals is as mysterious as when they were first described in 1853 by Charcot in the heart-blood and spleen of a

man who died of leukaemia. Leyden saw them in the asthmatic sputum twenty years later and since then they have been found in many conditions. Speculation as to their nature has been common; coagulation or crystallisation products of eosinophils, spermine and calcium are among the substances said to be implicated. It is certain however that these colourless, elongated octohedral crystals are most evident in diseases with an increase in the blood eosinophils. Examination of the blood smears of patients suffering from a variety of illnesses revealed no crystals in the blood even though the eosinophilia was as much as 25%; none of five patients with bronchial asthma had crystals in the blood while a case of ulcerative colitis had the crystals in the stools. On the other hand 2 out of 3 patients with chronic myelogenous leukaemia, one patient presumed to have periarteritis nodosa and another with trichiniasis, all showed numbers of crystals in wet smear preparations. Of 11 fatal cases of leukaemia only one had crystals in the tissues; these were present throughout the body but were most plentiful in the spleen and the pancreas.

An attempt to produce crystal formation in guinea pigs by inoculation with trichinia spiralis, which caused a 20% eosinophilia, failed. There is a judicious silence regarding the nature of the crystals except that they are soluble in a variety of common chemical substances, and that once destroyed they could not be reconstituted. So far, therefore, all we can say is that Charcot-

Leyden crystals are most likely to be found in asthma, periarteritis nodosa, trichiniasis, in certain intestinal infections and in localised collections of eosinophils such as nasal polyps and skin blebs; the claims that they are present in prostatic secretions and in normal blood are probably false. The feature common to these conditions is a high absolute or local eosinophilia and the association seems to be proven. It is possible that the isolation and chemical analysis of the crystals would prove of great help in the understanding of the eosinophil.

Thrombocytopenic Purpura.

(*Wiseman et al J. A. M. A.* 1940; 115; No. 1. 8).

Pathogenesis.

1. *The mechanism of the bleeding tendency:*—The recognised hematologic abnormality which always occurs in this disease is a marked reduction in circulating platelet level. Since the vital function of the blood platelet in the physiologic mechanism of blood clotting is well accepted, it would appear that the pathogenesis of bleeding is easily explained. Such however is not the case, for it has been occasionally observed that the platelets following the removal of the spleen in essential thrombocytopenic purpura may not be maintained at significantly higher levels and yet all clinical hemorrhagic manifestations disappear. Such atypical responses suggest a somewhat broader basic mechanism, namely (a) the platelet level in the blood may reflect or coincide, albeit imperfectly, with some other more

fundamental disturbance in the tissues of the body on which blood coagulation depends and which is influenced by splenectomy (this view has again been championed recently by Tidy (*B. M. J.* 1 : 583 1928), or (b) the bleeding tendency in this disease may be due to a combination of factors, of which the deficit in platelets is only one. Although it is always hazardous to speculate, it would seem that the second point of view is more likely to approximate the facts. Until there is a more satisfactory answer to such fundamental questions as to why the circulating blood remains fluid in the vascular system but coagulates promptly otherwise, the difficulties in understanding the exact mechanism of hemorrhage in every patient with purpuric manifestations becomes apparent. Obviously the precise role that the platelet plays in the pathogenesis of this disease must await the discovery of more facts that relate to the many other phases of the blood-coagulation problem.

Suggestions that the capillary bed may be at fault either because of increased permeability in addition to thrombocytopenia (*Pederson, J. Path & Bact.* 25; 94 Jan. 1922) or because of the inability of the capillaries to contract adequately [*MacKay, W; Quart. J. Med.* 24: 285 April 1931] provide attractive possible explanations for the cause of bleeding but in this disease are not supported by convincing experimental data. There is very little doubt that a defective endothelial structure may result in bleeding, but that

such defects are present in purpura hæmorrhagica have not been demonstrated. Nevertheless, the vulnerability of the capillary vessels must be a very important circumstance in preventing the loss of platelets and other blood elements to the tissues. The fact that some persons will show petechiæ with platelet counts of 100,000 or above, while others show no hemorrhage at platelet levels below 10,000 may be explained on this basis. The fact that the majority (not all) of the patients afflicted with this disease have a prolonged bleeding time has been cited as evidence of some obscure change in the capillary endothelium, but until all the factors which influence the mechanism of this test are known the significance of this observation must remain largely speculative.

No deficiencies in the soluble substances of the blood that have been found essential for blood coagulation can be demonstrated. The fact that the blood obtained in the active stages of this disease forms a clot that either retracts slowly or not at all, is directly traceable to the paucity in the platelet count. It is probably true that the failure of the clot to retract and squeeze out the serum results in a lack of firmness and impairs its value as a mechanical plug. This may be granted as a liability for effective hæmostasis and may be of far more importance in determining the bleeding tendency than is usually accorded to the phenomenon.

2. *The mechanism of Thrombocytopenia*:—(a) *The Spleen*: Kaznelson's designation of this disease as thrombolytische purpura describes what is now most widely held as the probable role played by the spleen in the pathogenesis of this disease. The belief that the spleen is chiefly responsible for the thrombocytopenia is due to two facts: (1) sternal marrow studies have consistently revealed normal numbers of normal appearing megakaryocytes in normal cellular setting, and (2) splenectomy has been followed by the prompt re-appearance of large numbers of platelets in the peripheral blood with the disappearance of all bleeding tendencies. Because it is difficult to demonstrate increased sequestration and phagocytosis of the platelets in the spleens removed from these patients, owing chiefly to the physical characteristics and the rapidity of lysis of these elements, the exact manner in which the thrombocytopenia is brought about is not regarded as entirely settled. Experience with the supravital technic in assaying the specificity of the phagocytic activity of the splenic clasmatoocytes as it relates to the various types of circulating blood accounts for the thrombocytopenia under these circumstances. A possible analogy is seen in the mechanism of the production of anæmia in congenital hemolytic icterus and in the recently discovered and described type of severe neutropenia due to excessive granulocyte phagocytosis by splenic clasmatoocytes. (Wiseman, B. K., and Doan, C. A.: A

newly recognized granulopenic syndrome caused by excessive splenic leukolysis and successfully treated by splenectomy read before the Thirty-First Annual Meeting of the American Society for Clinical Investigation, Atlantic City, J. Clin. Investigation 18: 473 July 1939. It is believed that lysis of effete platelets is perhaps a normal physiologic function of the spleen. An augmentation of this function at times until it has assumed pathologic proportions, appears most reasonable. Platelet counts obtained from the splenic artery and vein at operation have yielded inconstant results, but usually the platelet content of the venous blood has been definitely below that of the arterial blood. This has been true in our experience. The accuracy of this procedure in an organ which sensitively contracts on manipulation, discharging its cellular contents into the vein in unpredictable amount, however, is more than doubtful.

There still remains to be explained the fact that, although the platelets may increase in numbers promptly and symptoms subside with the removal of the spleen, the values for these elements may later fall to the original low levels, with reappearance of the bleeding diathesis. It is usually assumed that either hypertrophy of accessory splenic tissue with clasmatocytic endothelial system in other organs, such as the liver, in taking over the phagocytic function of the spleen also acquire the pathologic overactivity in destroying plate-

lets. This is a reasonable explanation but again lacks adequate supporting evidence. Others have interpreted this fact as invalidating the entire hypothesis of the splenic etiology of the thrombocytopenia in the disease. Frank advanced the theory that the spleen depresses, by some as yet unknown method of remote hormone-like control, the megakaryocytes in the bone marrow so that they are functionally unable to supply adequate number of platelets. Although this hypothesis cannot be disproved at present, many students of the disease feel that the explanation afforded by the evidence for the theory of splenic cytotoxicity is much sounder. Troland and Lee [Troland, C. E. and Lee, F. C.: Bull. John Hopkins Hosp. 62:85 Jan. 1938] have recently reported that extracts of spleens removed from patients with thrombocytopenic purpura contain a substance ("thrombocytopen") which, when injected into the experimental animal will depress the platelet levels. The attempted duplication of these experiments using monkeys and rabbits has so far failed to substantiate this work.

(b) *The bone marrow*:—No evidence has yet been presented which demonstrates any intrinsic pathologic condition of the bone marrow. The megakaryocytes are either normal or more often increased in numbers. Examinations of these cells in the living state in supravital preparations have revealed no qualitative defects. Cannulization of the efferent vein is probably the only decisive method of determining

the functional capacities of these marrow elements, but unfortunately this is not a practical procedure.

A mechanism which may result in peripheral thrombopenia has been suggested by the work of Madison and Squier [Squier, T. L., and Madison, F. W.: *J. Allergy* 8: 143 Jan. 1937]. Following their observations on the etiologic relationship between aminopyrine and malignant neutropenia, they noted that when patients with thrombocytopenic purpura were placed on elimination diets the blood platelets returned to normal levels. The fact that the megakaryocyte in some instances does become hypersensitive to specific allergens, particularly to drugs, cannot be doubted. These cases should be regarded as symptomatic thrombocytopenic purpura. In a series of cases tested by the method of Madison and Squier, there does not appear to be any relationship between the essential type of thrombocytopenic purpura as defined here and the allergic constitution.

Pathology.

Widespread hemorrhage, both gross and microscopic, is the only constant feature found in this disease at necropsy. Most observers have found the bone marrow to be normal. The spleen is usually normal and never more than slightly increased in size. Any case in which the spleen is easily palpated almost surely belongs to the symptomatic group of purpuras. The Nickerson and Sunderland series showed an

average weight of 227 gm. for six spleens removed surgically. The malpighian follicles were found to be enlarged and the germinal centres were active in all but two out of eleven specimens. [Nickerson, D. A. and Sunderland, D. A.: *Am. J. Path* 13: 463 (May 1937)]. Studies on the spleens removed surgically have consistently failed to reveal any noteworthy gross abnormalities. The largest spleen in a series of surgical cases weighed 230 gm., with an average of 124 gm. Nothing noteworthy was found on study of the paraffin sections. Megakaryocytes are likely to be found in various tissues of the body including the spleen, probably an embolic phenomenon.

Hematology.

Marked thrombocytopenia is the only constant hematologic feature of the blood. The bleeding time, while usually prolonged, has not infrequently been normal. The clotting time is normal but the clot usually fails to retract. The white cell count may be normal or there may be a mild or moderate increase in polymorphonuclear leukocytes, depending on the severity and recency of hemorrhage. The red cell count and degree of reticulocytosis depend directly on the amount of the blood loss. The tourniquet test is equally positive; occasionally, however, it is completely negative even when platelet values are very low.

There is no abnormality in the bone marrow except that which may reflect rapid and excessive

loss of blood. The megakaryocytes have never been numerically decreased or qualitatively altered in cases of true essential thrombocytopenic purpura.

Differential Diagnosis.

The separation of this disease entity from the host of other abnormalities that present bleeding with thrombocytopenia is often a difficult diagnostic problem. Failure to accomplish this successfully may result in disastrous therapeutic decisions and has, in general, cancelled, much of the statistical value of the literature. Less attention should be paid to the tourniquet test, clot retraction and bleeding times and more to the diagnostic features given below. The examination of the cellular content of the bone marrow is regarded as essential before final diagnosis is made in any given case.

Diagnostic essentials:

1. There must be spontaneous purpura and or free bleeding from the mucous membranes.
2. The blood platelet must be substantially decreased in numbers, less than 100,000 per cubic millimeter of blood.
3. The clotting time and prothrombin time must be within normal limits.
4. The anemia and leukocyte count must not be out of proportion to the amount of bleeding.
5. There must be no pathologic cells in either the blood or the bone marrow.

6. There must be no recent history of the ingestion of drugs or the occurrence of those diseases known occasionally to produce thrombocytopenia.

7. There must be no appreciable enlargement of the spleen or lymph nodes.

Course.

In the untreated case, the disease is often characterized by a cyclic course of remissions and exacerbations. Some patients may not have a recurrence of the disease after remission; others may be free for several years only to suffer a relapse later when they regard themselves permanently cured. In most cases, however, a more or less chronic state ensues with varying degrees of disablement. There does not seem to be any correlation between the severity of the bleeding episode and the subsequent course. In Wintrobe's (Wintrobe, M. M.; Hanrahan, E. M. Jr., and Thomas, C. B.: *purpura hæmorrhagica*, with special reference to course and treatment, *J. A. M. A.* 109: 1170 October 19, 1937) series (eighteen cases) the interval between the first bleeding episode and the second varied from one month to twenty-six years.

Treatment

There are few diseases in which the status of treatment has been so confused as the treatment of essential thrombocytopenia. This uncertainty has apparently been due to errors in differential diagnosis and to the failure to appreciate the remarkable tendencies

the disease has to subside spontaneously.

Medical. 1. *Radiant energy*: high voltage roentgen therapy over the spleen, first suggested by Stephen and more recently reviewed by Rudisill and others, has been variously reported as successful and unsuccessful. Experience convinces that it is worthless. Ultraviolet rays have been of no service.

2. *Snake venom*: The use of snake venom has been suggested both as a means of controlling hæmorrhage and as a prognostic test. For treatment, from 0.4 to 1 cc. of a 1:3000 mocassin venom is given subcutaneously twice a week. The prognostic test is performed by injecting from 0.1 to 0.2 cc. of a 1:3000 mocassin venom intracutaneously. The trend from positive to negative phase is said to be of value in estimating the trend of the purpuric state and the prognosis after splenectomy. Patients treated with snake venom without reversal of the positive skin test to negative are likely to obtain little benefit from surgery.

3. *Parathyroid extract*.—It was observed in a case of this disease in which a patient received an overdose of parathyroid extract consisting of 500 units in five days, all bleeding stopped. A second case was reported in 1936 in which 60 units of parathyroid extract plus calcium gluconate was given intentionally to a 7 year old boy with improvement clinically and hæmatologically. The treatment consists in giving

parathyroid extract plus calcium gluconate to the point of intoxication in which symptoms of vomiting, progressive weakness, apathy and lethargy predominate. This treatment has been tried without any favourable results.

4. *Elimination diets*.—This is discussed under pathogenesis. The suggestions of Madison and Squier have not been verified.

5. *Transfusion*.—The value of blood transfusions has been accorded wide acceptance, although Brill and Rosenthal have indicated that an increase of hæmorrhage may follow transfusion, especially in acute cases. Blood transfusion supplies not only lost plasma volume and red cells but adds also platelets presumably useful in controlling the loss of blood. The practical value of the latter may be open to serious question but of the former there can be scarcely any doubt. Transfusion has no effect in re-establishing the platelet equilibrium and therefore can in no sense be regarded as a curative measure but does serve the purpose of carrying the patient until a spontaneous remission sets in or of preparing the patient for operation so that the surgical risk will be less formidable. In some cases there is a variable hæmostatic effect exerted by the transfusions which may be effected from two to four days. Transfusions, when used, should be given in full dose (500 cc. for those of adult ages) and repeated as often as necessary to: (1) control excessive bleeding, (2) keep the blood pressure above 90 systolic and (3) maintain the red cell

count above 2,000,000. Citrated blood given by indirect technic is as effective as direct infusions of whole blood. Injections of blood intra-muscularly are not of value.

6. *Miscellaneous Measures*.—The injection of foreign proteins, calcium, proprietary coagulants, epinephrine and the like are without value in this disease. The use of viosterol by mouth has not helped. Intravenous injections or per oral use of ascorbic acid recently advocated has not been of service. The use of the vitamin substances B-2 and A and endocrine extracts, particularly thyrotropic hormone, needs confirmation.

2. *Surgical — Splenectomy*.—Since the demonstration by Kaznelson and Hess that splenectomy is regularly followed by a return of platelets to the blood stream and the cessation of bleeding, the constance of this therapeutic result has been amply verified. The dramatic results of removal of the spleen with cessation of hæmorrhage, often while the patient is still on the operating table, with a rise of platelets beginning immediately and more often than not reaching normal values in from twenty-four to forty-eight hours, leave one with little doubt that the measure is a specific and not a symptomatic one. The chief problem referable to splenectomy becomes a matter of individual judgment as to procedure based on the circumstances surrounding a given individual case. Here, as elsewhere, the wisdom of "treating the patient and not the disease" must not be neglected.

The essence of all medical management in this disorder is clearly one of sustaining the patient until a remission occurs. If bleeding does not subside or tend to diminish in the chronic case within a week it would appear unwise to delay surgery further, as it must be accepted as a cardinal principle in the management of this disorder that the more prolonged or violent the bleeding the more the danger of a sudden fatal termination through cerebral hæmorrhage or bleeding into some other vital structure.

The acute cases especially demand energetic action. Most authors warn against splenectomy in the acute phases of this disease. The incipient acute type as well as the acute exacerbation of the chronic type is an especial indication for urgent surgery, as a goodly proportion of this group will die otherwise. The procedure followed may be summarized as follows:

1. The diagnosis must be confirmed in all cases by bone marrow examination (puncture technic).

2. Blood transfusions are always given immediately if active bleeding presents.

(a) If this is effective in stopping hæmorrhage after a reasonable trial, delay in advising splenectomy is justified. If the platelet level determined daily, rises and continues to rise, plans for splenectomy may be temporarily or permanently abandoned, depending on subsequent improvement.

(b) If blood loss persists in acute cases in the same or in increased volume, splenectomy is not postponed further.

3. Splenectomy is indicated in:

(a) Chronic cases if free bleeding persists after a reasonable period of treatment with transfusions or when social or economic factors are important.

(b) Acute cases when transfusions are not immediately effective.

4. Splenectomy is contra-indicated in:

(a) Cases of doubtful diagnosis.

(b) Cases presenting a recent history of contact with certain drugs.

(c) Cases occurring during the active or convalescent stages of all infectious diseases.

(d) Cases in which the bone marrow shows depletion of the megakaryocytic content of the bone marrow.

Splenic Artery Ligation.—This procedure probably should never be attempted in purpura hæmorrhagica. Although the procedure may stop the bleeding, this is not to be relied on. The spleens in this disease are small and free from adhesions and are removed with very little more technical difficulty and risk to the patient than the procedure of ligation of the artery.

Prognosis.

The results vary markedly. Surgical deaths will inevitably

occur but should not exceed 5 per cent. The liberal use of blood transfusions pre-operatively, and post-operatively if required, the adequacy of differential diagnosis and good technical surgery should make possible this low operative mortality.

Calcium and Digitalis: (Szekely, P., *Lancet*, 1940 ii 761 letters to Ed.). The danger of giving calcium gluconate intravenously to digitalised patients has frequently been stressed and in view of the same the following is of interest.

The action of calcium on the cardiovascular system has been investigated by many workers both in animals and man. In dogs, the intravenous administration of calcium produces hypertension and vasoconstriction, its action being similar to that of sympathetic stimulation. Hazard and Wurmser explained this effect as being produced by a discharge of adrenaline, and they observed that in adrenalectomised dogs calcium injections had no effect on the vascular system. There was, besides a direct action on the heart muscle, producing increased amplitude of the auricular and ventricular contractions. This effect persisted even in adrenalectomised doses. Berliner pointed out that calcium has a direct effect on the myocardium in man, shown in the electrocardiogram by progressive changes in the P and T waves (inversion of P, flattening followed by inversion of T and by bradycardia). These changes were demonstrable four seconds after the end of the

injection. The T-wave change was the most constant, appearing in all but 0.2 per cent. of the cases; bradycardia came next in 67 per cent; and the changes in the P wave last, in 54 per cent. The changes were less marked when the injection was given slowly.

In clinical practice calcium injections are harmless, even in large amounts, when given slowly. The toxic effects arising from use of digitalis and calcium combined are due, in my opinion, to a raised digitalis action resulting from the synergistic effect of calcium and digitalis, so that the two drugs have an additive effect. Gold and Edwards in their studies on dogs arrived at the conclusion that hypercalcaemia greatly increases the susceptibility of the heart to the induction of idio-ventricular beats by ouabain. Billigheimer observed that intravenous calcium produced bradycardia, which reached its lowest point within 2 or 3 minutes and lasted up to 25 or 30 minutes. When the same injection was given to a digitalised patient, however, bradycardia lasted from 4 to 5 hours. Billigheimer explained the bradycardia as a vagus effect and supported this view by his observation that adrenaline tachycardia was stopped by calcium, while tachycardia produced by atropine remained unchanged.

Cases of congestive heart failure refractory to digitalis may show a considerable improvement when intravenous calcium gluconate is given as well. It is possible that in these cases there

is a transient disturbance of the calcium-potassium equilibrium which is restored by the administration of calcium. In a few cases of congestive heart failure refractory to digitalis treatment in which we determined the blood calcium, expecting to find hypocalcaemia, the calcium level in the blood serum was not much changed, but the level in the serum is not necessarily a reliable guide to the concentration in the tissues. On the other hand, in a relatively high proportion of cases of chronic nephritis hypercalcaemia is found, and congestive heart failure associated with chronic nephritis is often refractory to digitalis treatment.

Combined digitalis and calcium therapy may be beneficial in certain cases, but special care must be taken with the dosage of digitalis, because it cannot be predicted to what extent calcium will sensitise the heart muscle to that drug.

Cardiovascular Syphilis: (*Lancet*: Vol. II: 1940 P. 787).—The early diagnosis of syphilitic aortitis is as difficult as any in clinical medicine, and, as O'Farrell says, involvement of the aorta is so constantly present in cardio-vascular syphilis that the other forms may be disregarded with few exceptions. Most pathologists now agree that syphilitic involvement of the myocardium is exceedingly rare. Among recent attempts to make the diagnosis of early specific aortitis easier is that of Maynard, who gives the following six criteria to look for: (1) a definite history of syphilitic infection; (2) the absence of any

evidence of other disease that might dilate the aorta; (3) a patient aged 40 or less; (4) radiological evidence of dilatation of the aorta; (5) a hollow, accentuated aortic second sound; (6) a systolic murmur in the aortic area. O'Farrell rightly points out that the second of these criteria is often the most important, and the main difficulty here is the exclusion of the dilated, tortuous aorta of "arteriosclerosis." An enlarged left ventricle without aortic incompetence makes aortitis unlikely, but since an appreciable number of cases of specific aortitis are complicated by hypertension the final decision may not be easy. A valuable point which O'Farrell does not mention is the increased density of the aorta detectable on screening in many syphilitic cases. The late stage of aortitis—aneurysm of the aorta—is as a rule easier to diagnose, especially if radiology is employed in all cases of suspected heart disease or pain in the chest, though the time-honoured classification of aneurysms into those of signs and those of symptoms has now had a third category added to—those with neither signs nor symptoms. O'Farrell suggests that aneurysm of the first part of the aorta is particularly difficult to diagnose, but actually these are the cases in which the aortic valve is most likely to be involved and it is usually not long before an aneurysm in this area shows itself by pulsation in the chest wall. A commoner difficulty lies in mistaking pulsation to the right of the upper part of the sternum due to aortic incompetence for an aneurysm. It is

regrettable that O'Farrell supports the old teaching that it is possible to differentiate between the murmurs of rheumatic and syphilitic aortic incompetence by their site, the former being supposed to be maximal to the left of the sternum and the latter to the right. The relationship of syphilis to coronary disease deserves further investigation especially in these days when doctors are becoming so coronary conscious. In the past we may have been too apt to attribute symptoms and signs to syphilis, but so far as coronary disease is concerned we are now swinging too far in the opposite direction.

Consideration of cardiovascular syphilis leads to one certain conclusion—that prevention is easier than cure, and that the first essential is to treat every syphilitic efficiently at the time of primary infection. As a further precaution all people who have had such an infection should have their heart examined, clinically and radiologically, once or twice every year.

Hypertension and the Surgical Kidney: (*Lancet* Vol. II, 1940: Page 687.) It now seems certain that experimental renal hypertension depends on the operation of chemical or humoral factors, the degree of response being perhaps controlled by the endocrine glands. Evidence has pointed to renin as the responsible pressor substance; thus it is found in excessive amounts in the venous blood of kidneys which have been rendered ischaemic either by the Goldblatt clamp or by other experimental means. According to

Page and his co-workers, however, purified renin is not a true pressor substance. They have produced evidence that renin acts as an enzyme on a substrate ("renin-activator") which is normally present in the blood to produce "angiotonin" which has a strong pressor effect on the peripheral vessels, more lasting than that of adrenaline. Further they have isolated angiotonin as a crystalline oxalate and picrate and find that it is water soluble, heat-stable, dialysable and fluorescent, and gives like arginine a positive Sakaguchi reaction. The pressor effects attributable to unilateral renal ischaemia are, however, known to be mitigated by the intact kidney; the normal blood-pressure thus presumably represents a balance reached by the interaction of pressor and antipressor mechanism initiated by the kidney.

Crude renal extracts have long been said to contain antipressor substance, but until recently such claims have received scant consideration. Page and others now find that extracts either of fresh kidney or muscle given by subcutaneous or intramuscular injection, or by mouth, will reduce arterial pressure in dogs and rats. These extracts when given to eight human subjects with essential or malignant hypertension caused a sharp and prolonged fall in arterial pressure, followed by a rise when the extracts had been withheld for from 3 to 5 days. These observations agree with those of Williams, Harrison and Grollman who demonstrated the capacity of re-

nal extracts to inhibit the pressor action of renin and to reduce the blood pressure in hypertensive states. These latter workers have now reported the effects of oral administration of renal extracts to a small number of hypertensive patients two of whom are specified as suffering from malignant hypertension. A considerable fall of blood pressure was observed during the period of therapy and this was accompanied by a subjective improvement in symptoms. Encouraging as these first trials have been a cautious approach to this form of treatment is necessary. As Grollman and his colleagues point out, the desirability of reducing blood pressure may be questionable; in their experimental animals vomiting and other toxic effects were observed after treatment. Such effects may be due to some impurity in the extracts, which are admittedly crude. They also point out that the subjective improvement in their patients may have been due to the effect of suggestion and that further work is necessary to exclude the possibility that the declines in blood pressure were spontaneous. Theoretically the administration of renal extract should be effective only in subjects suffering from hypertension of renal origin. How far experimental hypertension in animals provides the key to the problem of essential and malignant hypertension in man is still undecided, but all these observations have a bearing on the class of case in which a chronic lesion has produced pronounced ischaemia of one or both kidneys.

Sufficient evidence has accumulated to show that hypertension complicating chronic unilateral pyelonephritis may be relieved by the removal of the affected kidney. But the incidence of hypertension amongst those suffering from pyelonephritis is not high. How far the association of pyelonephritis and hypertension is fortuitous and to what extent does kidney disease precipitate the onset of hypertension in a person already predisposed to this disorder are not known. As a result of investigations by Palmer et al the recommendation is that nephrectomy should be restricted to women under forty-five and men under fifty since hypertension of unknown etiology is likely to appear later on. The younger the patient and the more recent the onset of hypertension the better is the chance of a favourable result.

Ptosis of the kidney may also be complicated by hypertension but no estimate is yet available of the frequency of his association. The hypertension was relieved by recumbency and in this posture the renal blood flow as measured by the plasma diodrast clearance and haematocrit, was increased. This condition has been named 'orthostatic hypertension'. Nephropexy and wearing of a special belt gave relief of symptoms but not material lowering of the blood pressure. The part of posture as a part of routine examination of hypertensive subjects for periods from two to five days should be explored.

The association of renal tumours with hypertension acquires a

fresh interest when considered in the light of recent work on experimental renal ichaemia. Compressing tumours might be expected to exert effects similar to those produced by other ischaemic mechanisms, and instances are on record in which hypertension has been relieved by nephrectomy.

To what extent venous obstruction may pave the way for hypertension is uncertain. In a case published, thrombosis of inferior vena cava and both main renal vessels complicated whooping cough in a boy of nine and was followed by gross hypertension ending in heart failure four years later. Autopsy revealed extreme atrophy of the left kidney and hypertrophy of the right kidney. Survival of this right kidney was determined by a patent aberrant vein which entered the vena cava above the level of thrombosis. Whether the hypertension was due to the destruction of the left kidney or to interference with circulation with the right remains an open question.

Therapeutic Aspects of Hemophilia: (D. ARTHUR, J. PATELL, JR. *J.A.M.A.* Vol. 115 P. 211.) The measures advocated for the treatment of hemophilia may be separated into empirical therapy and rational therapy. The first group includes measures that have been tried because they were shown to be effective in other conditions that resemble hemophilia in certain aspects of their symptomatology, and include the administration of vitamin concentrates, calcium salts, extracts from liver, lung,

placenta and bone marrow, and numerous other preparations.

The rational therapy for hemophilia or, indeed, for any disorder depends on an understanding of the etiology of hemophilic disease. Obviously the etiology of hemophilia is related to an inborn fault. Since hemophilia is sex linked, it is supposed that the disease might be related to an endocrine defect. With this in mind Birch and others administered ovarin substance and female sex hormones to patients with hemophilia. Subsequent trial of this therapy by others has been disappointing. Moreover there was little if any, evidence that patients with hemophilia lacked estrongenetic substances. Nevertheless it may well be that there is a regulator for the clotting mechanism which in some manner is related to the sex hormones. The regulation of salt metabolism by the adrenal cortex might serve as an analogy.

In recent years attention has been directed to the blood clotting mechanism itself, which appears to be the immediate locus of difficulty. The various studies of the problem agree that the clotting of hemophilic blood is retarded. The retardation of clotting appears to take place in the first phase or in the conversion of prothrombin to thrombin. There are differences of opinion concerning the fault at this point. Some investigators attribute the delay to a qualitative change in prothrombin, others to the lack of available thrombo-plastin, still others to the lack of an unknown

substance which is present in normal plasma and which may be precipitated with the globulin fraction of the plasma. Certain workers incriminate the blood platelets while others believe that the clotting defect bears no essential relation to the blood platelets. From the point of view of treatment these differences of opinion are of no immediate concern. However, from these various studies several practical measures for the treatment of hemophilia have evolved.

These measures are based on the observation that transfusion with normal blood shortens the hemophilic clotting time. The maximal effect from transfusion is almost immediate. In the course of from eighteen to forty-eight hours there is gradual return of the clotting time to its original abnormal value. The transfusion with 100 cc. of blood is as effective as the transfusion with 500 cc. Therefore, unless the patient urgently needs hemoglobin, a transfusion of 100 cc. of blood at twelve hour intervals is preferable to a transfusion 600 cc. at three day intervals.

Transfusion of normal citrated plasma is also effective in reducing the clotting time of hemophilic blood. There are certain advantages in its use. It may be stored for weeks in the ice box without appreciable change. It may be administered without regard to blood groups. No untoward reactions have followed the repeated administration of 100 cc. of pooled plasma. When using plasma for this purpose it is advisable to take the precaution

of passing it through the Berkefeld filter to remove particulate matter.

In the treatment of superficial bleeding, as from the nose or tooth sockets, the local application of certain tissue extracts and of blood derivatives has been shown to be of help. Perhaps the most potent of these are the dried "globulin substance" and dried thrombin. These substances are stable in dried form. They are obtainable from animal sources. If these are applied in powdered form to the surface of moistened gauze and packed against the bleeding point, they are usually effective. A dry or powdered preparation is preferable to a liquid because it is not washed away so readily by the oozing blood.

There are several clinical features of the disease to be stressed, since they are not usually emphasized. The first of these relates to intercurrent infections. It is very common to observe bleeding episodes occurring either with infection or several days after the onset of infection. Indeed the bleeding may be with rhinitis, or retropharyngeal bleeding with pharyngitis, or bleeding gums with abscessed teeth. It is sometimes said that hemophilia is milder in summer than in winter. This seasonal variation in hemophilia more probably is due to the upper respiratory infections in winter.

The commonest complication of hemophilia is hemarthrosis. When this occurs, small transfusions should be given for several

days to prevent further bleeding. The joints become swollen, tender and painful. If bleeding extends into the tissues about the joint, the overlying skin becomes warm and discoloured. Pain and discomfort are alleviated by the administration of salicylates and by immobilization of the joints. After the acute symptoms subside, gentle massage, radiant heat and active motion may be tried. The ankyloses and deformities resulting from hemarthroses are due in part to the premature resumption of joint motion.

Surgical emergencies present the most difficult decision. Hemorrhage in the submucosa of the posterior pharynx, in the body of the tongue or in the tissues of the neck may all but strangle these patients. However, counter-pressure from the distended tissues generally checks the bleeding in these areas. In such instances it is best to give transfusions and avoid surgical intervention. The simplest and safest rule to follow is to avoid surgical procedure unless it is unavoidable. Under such circumstances it is essential to prepare the patient by transfusions both pre-operatively and post-operatively.

Therapeutic Aspects of Hemorrhagic Diseases in Infancy and Childhood: Dr. OSCAR M. SCHLOSS, (*The J.A.M.A.*, Vol. 115, P. 213).—During the first few days of life, usually from the second to the fifth, the new born infant may develop spontaneous hemorrhage. There is great irregularity in the source of the bleeding and its severity. It may originate in the

skin, subcutaneous tissues, viscera, serous membranes or cranial cavity. Often the degree of hemorrhage is slight and the bleeding may cease spontaneously within a short time. At the other extreme, death from exsanguination may occur within a few hours.

The best treatment is the administration of human blood. Whole blood may be given by intramuscular injection, but unquestionably transfusion is the method of choice. Transfusions of about 10 cc. of blood per kilogram of body weight are usually adequate and may be repeated in from one to three days if indicated.

Transfusions serve two purposes: (1) the replacement of lost blood and (2) the relief of the tendency to bleed. Citrated blood always fulfils the first requirement and usually both, but occasionally it is necessary to give unmodified blood by direct transfusion to control the bleeding tendency effectively.

Within the last few years, evidence has accumulated which indicates that vitamin K deficiency may be a factor in some cases of spontaneous hemorrhage in the new born. It has been noted that in the new born prothrombin has only from 14 to 39 per cent. of the values found in adults. More important are the observations that the prothrombin falls to an even lower level sometime between the second and seventh days of life, the period during which hemorrhage is most apt to occur. A few cases have been

reported in which abnormally low prothrombin of bleeding infants was raised to normal by the administration of vitamin K, with coincident cessation of bleeding. Much further evidence is necessary to clear the possible relationship of vitamin K deficiency to hemorrhagic disease in the newborn.

If it is demonstrated that vitamin K deficiency is the usual or even a common cause of bleeding in the newborn, prophylactic treatment will probably become universal. Hellman and Shettles have shown that the administration of large doses of vitamin K to the mother, even shortly before the infant is born, can raise the infants' prothrombin to three times the average value.

Meanwhile the administration of vitamin K or an effective chemical substitute (methyl-1, 4-naphthoquinone) in addition to blood transfusions would seem a rational procedure. It would naturally be best to do this under the guidance of prothrombin time determinations, but even if this is not possible vitamin K may be given empirically in all cases of severe or persistent hemorrhage.

The conditions for which vitamin K therapy in surgery are particularly useful are the hemorrhagic tendency in jaundice and the similar tendency which may occur in the presence of severe liver disease. It is now accepted that any patient with a plasma prothrombin level below 60 points on the Smith scale or 70 points by the Quick test should receive vitamin K. Prothrombin defi-

encies are much more widespread than one would think but usually are not of such severity as to be critical. However, after surgical operations and after hemorrhage, the body and compensatory mechanism for maintaining blood volume may dilute the prothrombin to a critical point. In patients who, because of gastric ulcer or carcinoma, have been on a markedly deficient diet before operation, the operation itself may depress the prothrombin still further, and this plus an inadequate vitamin intake following the operation may cause the prothrombin level to fall below the point at which hemorrhage occurs.

As far as the actual therapy is concerned, several methods can be used. Vitamin K can be given by mouth with bile salts if the latter are not present in the gastrointestinal tract, but I think that the method which will come to be used from now on is the administration either by mouth with bile salts, if necessary or hypodermically of synthetic naphtha quinone derivatives, either the 2-methyl-1, 4-naphthoquinone or the compound which contains a phytol group in addition. This substance is tremendously potent so far as its prothrombin forming activity is concerned. In a newborn child 0.5 mg. produces a corresponding rise. One mg. in a dog will elevate the plasma prothrombin level as much as 50 points and keep it elevated for two weeks. Further more, there is a wide gap between the therapeutic and the toxic dose of this material. It requires something on

the order of 2 mgm. per kilogram to produce toxic effects in animals, and a total dose of 1 mg. a day in an adult is entirely adequate. The substance can be injected in corn oil for slow absorption or the dipropionate can be injected in twice the amount, that is 2 mg. subcutaneously. A very comforting point is the fact that no matter how much vitamin K is given subcutaneously, orally or even intravenously, the prothrombin can never be forced above 100 per cent. of normal by that method.

The Action of Digitalis: (B. M. J. 17 August 1940).—Till the beginning of this century digitalis was believed to be diuretic, but this is now regarded as a secondary effect of improved circulation. The beneficial effect upon the heart was attributed among other things to slowing, allowing of more diastolic recovery, and to correction of overdistension. Gold and Catell (Arch. Int. Med. 1940 65: 263) point out that the improvement may occur without slowing, and that the physiological response to effort is a quickened beat, while Wiggers (Amer. Heart Jour. 1936: 11: 273) says that a normal heart may beat up to a rate of 200 before the circulation begins to fail. Slowing is therefore the result and not the cause of the improvement. As to cardiac overdistension, Starling's law of the heart enunciates that its systolic energy is proportional to the degree of previous diastolic stretching. Normally the dilatation is a physiological response to increased work. It had therefore to be assumed that

a critical point is reached, presumably caused by high venous pressure in a diseased heart, above which this adaptive mechanism failed, and digitalis was said to enable this overstretched muscle to shorten again. But MacMichael found that diseased hearts are less susceptible than normal ones to increments of venous pressure, and the experimental evidence is against the idea of overstretching.

When the nature of auricular fibrillation was revealed by the electrocardiograph and it was noted that digitalis diminished conductivity in the auriculo-ventricular bundle while much alleviating symptoms, it was declared by enthusiasts that the sole effect of digitalis was on conductivity and that therefore its only therapeutic value was in auricular fibrillation. It was several years before cumulative clinical experience was able to overthrow this dogmatic assertion, which received its final blow when Peters and Visscher demonstrated that under digitalis, heart muscle not only puts out more energy but it utilizes it more efficiently, converting more into external work. Gold and Catell measured the tension with isometric lever on the isolated papillary muscle of a cat's heart immersed in Ringer's solution, and found that all digitalis glucosides improve systolic tension while the diastolic tension remained normal. They observed in the isolated heart-lung preparation that under digitalis the heart loses potassium and that there is a relative increase in its calcium

content. This is a most interesting observation for several reasons. Gaskell long ago showed the depressing effect of potassium on the frog's heart which could be ultimately reduced to diastolic stand still in the same position as that reduced by vagal stimulation. Years later, Zondek maintained that excitation of the vagus can be produced by increased concentration of the potassium ion. Long before that Locke had shown that the addition of calcium to Ringer's solution much improved its influence in maintaining the heart beat in perfusion experiments. And in the discussion at a recent meeting of the association of Physicians, stress was laid on the importance of not giving potassium salts in cases of, failing heart. In addition to this confirmation of experimental and clinical observations it is further evidence of a new light which is being thrown on many problems, by a study of mineral metabolism and of the close association of chemical and nervous mechanisms which has been a striking generalisation in this century.

The conclusion seems to be that digitalis improves the function of the heart in cardiac failure by direct action on the muscle without primarily changing its diastolic length, and accomplishes this through a bio chemical change in its mineral metabolism. This does not dispose of its usefulness in also blocking the way to irregular stimuli from auricle to ventricle in auricular fibrillation.

Service News and Notes.

In our circular letter of the 5th March 1941 calling for members' opinion on the proposed change in designation of members of the Madras Medical Service members were informed of the proceedings of the Annual General Meeting on the 20th December 1940 and of the personnel of the Executive Committee etc. for 1941.

There was no widespread desire for the proposed change in designation. The Executive Committee sent a reply to the Surgeon-General in accordance with the bulk of opinion received and expressed at their meeting.

We have to record the retirement from active service of the following members since our last issue:

Dr. K. M. Mathulla from 1-1-41.

Dr. K. Gopal Rao from 24-2-41.

Dr. S. Kantimathinathan from 1-4-41.

Rao Saheb Dr. S. Venkatasubba Rao from 13-3-41.

Dr. V. Krishnamurti from 16-5-41.

We wish these officers well of the rest they have earned. We hope that they will continue to support their old service association.

We regret to record the premature and sudden death while on active service of Dr. P. M. Varughese at Chittoor on the 4th April 1941. We have not recovered yet from our grief at the death of our distinguished Professor of Anatomy Dr. P. K. Koshi in March 1941. Our hearts go out to the members of the bereaved families.

We have great pleasure at the appointment of Drs. Rao Bahadur P. Krishnaswami, Rao Bahadur M. J. Santana Krishna Pillai and Rao Saheb S. Venkatasubba Rao to the consulting staff of the General Hospital, Madras. We congratulate too Dr. M. J. S. Pillai on the well merited title of Rao Bahadur conferred on him.

We are proud of Dr. M. G. Kini over the Fellowship of the Royal Society of Edinburgh to which he has been elected. We trust that this is only a prelude to further recognitions abroad.

We congratulate Dr. V. Thayumanaswami on the degree of M. S. that he has just earned.

We publish below for members' information and guidance copy of Press Note No. 49, dated the 7th April 1941 of the Government of Madras, Department of Education and Public Health, with Annexures I and III, and covering letter R. No. 13125

Establishment 29-4-41 from the Surgeon-General to our President. We trust that members will avail themselves of the opportunities afforded by Government.

Copy of the letter R. No. 13125/Establishment dated 29th April 1941 from the Surgeon-General with the Government of Madras, to the President, the Madras Medical Association.

"Sir,

I enclose herewith a copy of the press note dated 7th April 1941 regarding recruitment of Medical Officers for the defence department for your information. It is requested that you will kindly bring it to the notice of the medical practitioners of the Presidency, so that they may volunteer in sufficiently large numbers and avail themselves of the concessions extended to them by the Government."

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Government of Madras—Education and Public Health Department.

The following Press Note is issued.

PRESS NOTE No. 49.

Dated Fort St. George, 7th April 1941.

Owing to the War more doctors are required for the Army. Emergency Commissions are being given in the Medical Services and the Defence Department is inviting applications for these Commissions. A summary of the qualifications prescribed for the grant of Commissions and the pays and allowances admissible to candidates selected are set out in Annexures I and II. If further or more exact information is required, it may be obtained by application to the Surgeon-General, Madras.

2. Candidates with high qualifications who are granted Emergency Commissions in the Indian Medical Service will be eligible for an antedate as explained in Annexure III which would entitle them to more rapid promotion to the rank of Captain.

3. Civil Medical Officers employed or to be employed under this Government and deputed for military duty have been granted the following concessions:—

1. They will retain their lien in the Civil Department.
2. If they are probationers they will be confirmed on the occurrence of suitable vacancies;
3. The period of military service will count towards probation, pay and promotion; it will also count for civil pension if the officer holds a substantively permanent post in the Civil Department.
4. The period spent on field service will count—
 - (a) double for probation and increment of pay.
 - (b) for accumulation of leave under the Civil Rules, leave if any taken while on Military duty being deducted.
4. It has been suggested that qualified doctors who are not already employed in the Civil Department should also have opportu-

nities of serving the Defence Department with the prospects, if possible, of being absorbed in the Civil line on reversion from the Defence Department. The Madras Government have, therefore, approved the following arrangement for recruitment in this Province:—

- (1) Substantive vacancies in the provincial cadres of sub-assistant surgeons and civil assistant surgeons will not, except in special circumstances, be filled during the continuance of the War. Candidates selected for the Military Department will first be appointed to the provincial cadres and then be deputed for duty in the Defence Department.
- (2) Candidates with good War service will be given preference in the matter of retention in officiating vacancies and confirmation in substantive vacancies occurring in the Civil Department, in the order in which they proceed for duty in the Defence Department.
- (3) The number of candidates to whom it would be possible to extend such preference will be settled periodically with reference to prospective vacancies.

5. Service rules relating to the Madras Medical Service and the Madras Medical Subordinate Service have been amended implementing these decisions and the amendments notified at pages 252-253 of Part 1-A of the Fort St. George Gazette dated the 1st April 1941.

6. The Government trust that medical practitioners and also persons who have recently taken or are about to take their medical degrees will avail themselves of the opportunities which now exist for a career both during and after the War with the possibility in suitable cases of obtaining permanent commissions in the Medical Services.

E. C. WOOD,
Secretary to Government.

ANNEXURE I.

Emergency Commissions in the Indian Medical Service during the War.

Qualifications for Appointment.

In order to be eligible for consideration an applicant must—possess a medical qualification registered in Great Britain and Northern Ireland under the Medical Acts in force at the time of his appointment or an Indian Medical qualification recognised under Section 11 (i) of the Indian Medical Council Act, 1933, and registered in British India under one of the Provincial Medical Acts.

Pay and allowances.

The issue of pay and allowances is subject to the general conditions prescribed in the Pay and Allowance Regulations for the Army in India.

The following are the monthly rates of basic and overseas pay payable from the date of joining for duty :—

Rank and service in rank.	Basic pay in Rs. per mensem.	Year of Service.	Overseas pay in Rs. per mensem for service beyond limits of India but not including Burma.
Lieutenant	450	1	150
Captain, during 1st year as such	500	2	250
Captain, during 2nd and 3rd years as such	550	{ 3 4	250 250
Captain, during 4th year as such	600	5	250
Captain, during the 5th year as such	600	6	300
Captain, during the 6th and 7th years as such	700	{ 7 8	300 300
Captain, during the 8th and subsequent years of service as such	700	{ 9 10 11 12 and subsequent years.	350 350 350 400

Annexure II deals with the emergency branch of the L.M.D. (S.A.S.) and is omitted here.

ANNEXURE III.**Conditions for the grant of antedate in Commissions granted.**

(i) An antedate not exceeding one year may be granted to a candidate who, at the time of selection, has taken one of the following higher qualifications: (1) M. D. or M. S. or its equivalent such as M. Ch., etc., of a University of the British Empire whose qualifications are registrable in Great Britain; (2) F. R. C. S., England, Edinburgh or Ireland; (3) M. R. C. P., London, Edinburgh or Dublin, and F. R. F. P. and S. of Glasgow; provided that (a) the regulations require the candidate, subsequently to taking his medical qualifications to hold a resident hospital appointment for one year, or to engage in post-graduate study at a recognised medical institution

(not to include ordinary practice of his profession) for a period of two years before he is qualified to sit for the examination for the higher qualification; or (b) in the case of any of the above-mentioned qualifications not necessitating the post-graduate work mentioned under (a), the candidate for a commission shall, in addition to having taken such higher qualification, produce evidence to the satisfaction of the Director-General, Indian Medical Service, that he has actually engaged in equivalent post-graduate study.

(ii) An antedate not exceeding six months may be granted to a candidate who, at the time of selection, is in possession of a Diploma of Public Health registered by the General Medical Council or of a qualification recognised by the General Medical Council as in all respects equivalent to the Diploma of Public Health and as involving a similar period of post-graduate study.

In addition to pay, officers who are appointed to hold certain posts will be granted additional pay as shown below :—

Specialist pay at Rs. 100 per mensem will be admissible to an officer who is appointed as specialist in :—

Advanced Operative Surgery.

Medicine.

Ophthalmology.

Gynæcology and Midwifery.

Dermatology including Venereal diseases

Anæsthetics.

Mental diseases.

Radiology.

Otology, Laryngology and Rhinology.

Command pay as detailed below will be admissible to an officer appointed as officer commanding, or as Second in command of an Indian Military Hospital.

Class of Hospital.	Command. Rs.	Second in Command. Rs.
1st Class	240	120
2nd "	180	90
3rd "	120	nil
4th "	60	nil

Charge pay varying from Rs. 30 to Rs. 240 per mensem will be admissible for the medical charge of staffs of certain stations, depots, factories, etc., and at Rs. 60 per mensem for an officer in charge or a Brigade Laboratory.

For holding charges of a Cantonment Hospital or Cantonment Dispensary an officer will be eligible for such allowance as may be approved by the Cantonment authorities concerned and sanctioned by the General Officer Commanding-in-Chief, the Command.

Note.—The above rates are liable to change from time to time.

Outfit allowances.—An officer who has not previously drawn any outfit allowance from Government will be granted on appointment an allowance of Rs. 400.

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IN MEMORIAM.



By the untimely death of the late Prof. P. K. Koshy on 19th March 1941 the Madras Medical Service has lost one of its most eminent members, the Central Institute of Anatomy, Madras, a very capable and conscientious teacher and his family a most beloved and affectionate head. Prof. Koshy's was the unique distinction of being the first South Indian to be conferred the Fellowship of the Royal College of Physicians, Edinburgh.

Prof. Koshy will ever be remembered by the present and future generations as the driving force who brought the Anatomy Department to its present state of great efficiency, especially as the founder of a thoroughly up-to-date museum in Anatomy. This museum was the life work of the Professor and it has exacted the highest admiration of all visitors, including the censors of the Royal College of Surgeons from England.

As a teacher Prof. Koshy was very painstaking and conscientious. He knew every student of his class by name and followed up his progress. He would pick out the backward students and paid particular attention to them, and would not rest till they were brought up to the general standard of the class.

As a man Prof. Koshy was very simple, austere in his habits, sincere in his dealings and affectionate in his nature. Except for an occasional irritability, very often of momentary duration, he was one of the most lovable of personalities. His motto was work, continuous work, and he went out of this world working.

So long as the Anatomy Department and the Anatomy Museum of the Madras Medical College exist the name of Prof. Koshy will be remembered and cherished among all.

Let his benevolent spirit rest in peace.

P. V. F.

Bombay Medical Council.

The following summary of the proceedings of the Meeting of the Bombay Medical Council held under the presidency of Major-General R. H. Candy, C.I.E., K.H.S., M.B.B.S., M.R.C.S., L.R.C.P., I.M.S., J.P., on the 10th February 1941 is published for general information :—

The Council elected the following six members for the Executive Committee for the year 1941-42 :—

Lieut.-Col. S. L. Bhatia, M.C., M.A., M.D., I.M.S., J. P.

Dr. B. G. Vad, M.D., F.C.P.S.

Dr. C. A. Amesur, M.S., M.R.C.S., L.R.C.P.S., D.L.O.

Dr. George Coelho, M.B.B.S., M.R.C.P., B.Hy.

Dr. U. B. Narayanrao, L.C.P.S.

Dr. V. D. Sathaye, B.Sc., L.C.P.S.

With regard to the adjourned consideration of complaint against Dr. J. J. Cursetji, M.D., L.R.C.P. & S., etc., in respect of the publication of an article in the *Insurance World* of February 1939 and several statements made therein, it was decided that Dr. Cursetji's letter of explanation and regret be accepted and the papers recorded.

It was decided that the consideration of the complaint against Dr. J. P. Chobhe, M.B.B.S., Nasik, for infringement of the provisions

of Clause 1 (b) of Section II of the Code of Medical Ethics as per the resolution of the Executive Committee in that behalf, be adjourned to the next session of the Council.

With reference to the Report of the Sub-Committee in respect of the Notice of Motion by Dr. Jivraj Mehta regarding amendment in Section 3 of the Schedule to the Bombay Medical Act, 1912, and the memorandum from the Surgeon-General with the Government of Bombay and its accompaniments, on the question of recognition of medical degrees by Provincial Medical Councils, of Licensing Bodies outside British India, pending amendment of the Indian Medical Council Act, 1933, investing the Medical Council of India with powers to have an All India Register, it was decided that the object the Medical Council of India had in view could best be achieved by Central Legislation on the subject, and pending the same, by the Provincial Medical Councils recognising for registration qualifications laid down in Schedule II of the Medical Council of India Act, 1933, only. It was also decided to recommend to Government that pending the proposed legislation by the Government of India regarding amendment of Indian Medical Council Act, 1933, on the question of recognition of Licensing Bodies outside

India, qualifications of all non-Indian Licensing Bodies not on the Second Schedule to the Medical Council of India Act, 1933, be deleted from the Schedule to the Bombay Medical Act, 1912.

The recommendations of the Sub-Committee in respect of the Notice of Motion proposed by Dr. Gadgil and seconded by Dr. Coelho regarding amendments in the Rules of the Council relating to selection were accepted subject to certain amendment being incorporated therein.

The Committee's recommendation in respect of a resolution adopted by the Council relating to the amendment of the Bombay Medical Act, VI of 1912, was accepted.

It was decided that having regard to the practice obtaining in other Provinces, the courtesy title of "Dr." should be prefixed hereafter in the case of all medical practitioners registered under the Bombay Medical Act, 1912.

The motion of Dr. U. B. Narayanrao expressing the Council's opinion that in order to have a uniform Code of Medical Ethics for the whole of India, the Medical Council of India be requested to convene a representative Conference of all the Provincial Medical Councils or Boards constituted under an Act of Provincial Legislature, was lost.

It was decided that the papers relating to the application of

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Mr. R. M. Thaker for registration of his name under Section 7 (3) of the Bombay Medical Act, 1912, be referred back to the Executive Committee for further investigation and report.

With reference to the memorandum from the Surgeon-General with the Government of Bombay requesting the views of the Council on the proposed amendment to the Government Resolution, General Department, No. 7898, dated 6th November 1939, relating to the registration of persons holding qualifications from the College of Physicians and Surgeons, Calcutta, in 1909, it was decided that no amendment in the orders contained in the Government Resolution was necessary and that such cases of those practitioners only who are domiciled in the Province of Bombay or Sind should be considered hereafter.

It was decided that in the opinion of the Council for paragraph 1 (1) of Government Resolution, General Department, No. 7898, dated 6th November 1939, regarding recognition of qualifications of certain Calcutta institutions obtained between the years 1912 to 1916 (both inclusive), the following be substituted:—

"The National Medical College and the National College of Physicians and Surgeons, Calcutta."

With reference to the letter from the Surgeon-General with the Government of Bombay requesting the views of the Council

Bombay Medical Council

the question of proposed legislation to amend the Indian Medical Council Act, 1933, in order to empower the Council to appoint "Visitors" in addition to inspectors, it was decided that the proposed legislation respecting the appointment of visitors by the Medical Council of India, was not necessary.

9, New Marine Lines, }
Bombay.
25th February 1941. }

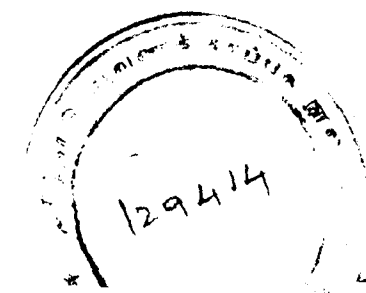
The resolution given notice of by Dr. Mrs. K. Tarabai, seconded by Dr. Amesur, regarding proposed amendment of some provisions of Clause 1 of Section II of the Code of Medical Ethics relating to certain Objectionable Practices, was referred to the Executive Committee for report.

AMBALAL P. PARIKH,
Registrar,
Bombay Medical Council.

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—*Lancet*, 1940 ii 664.



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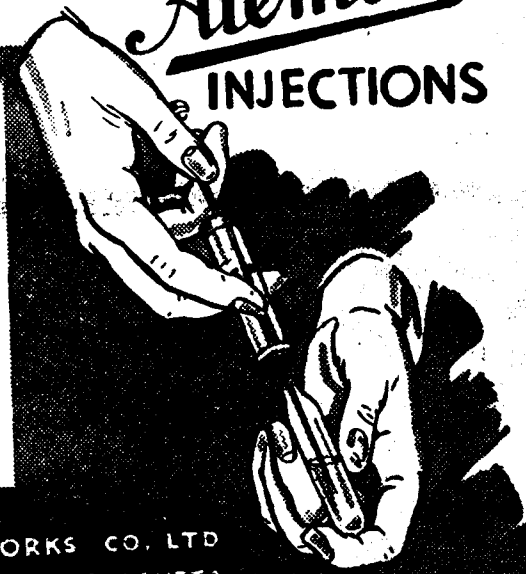
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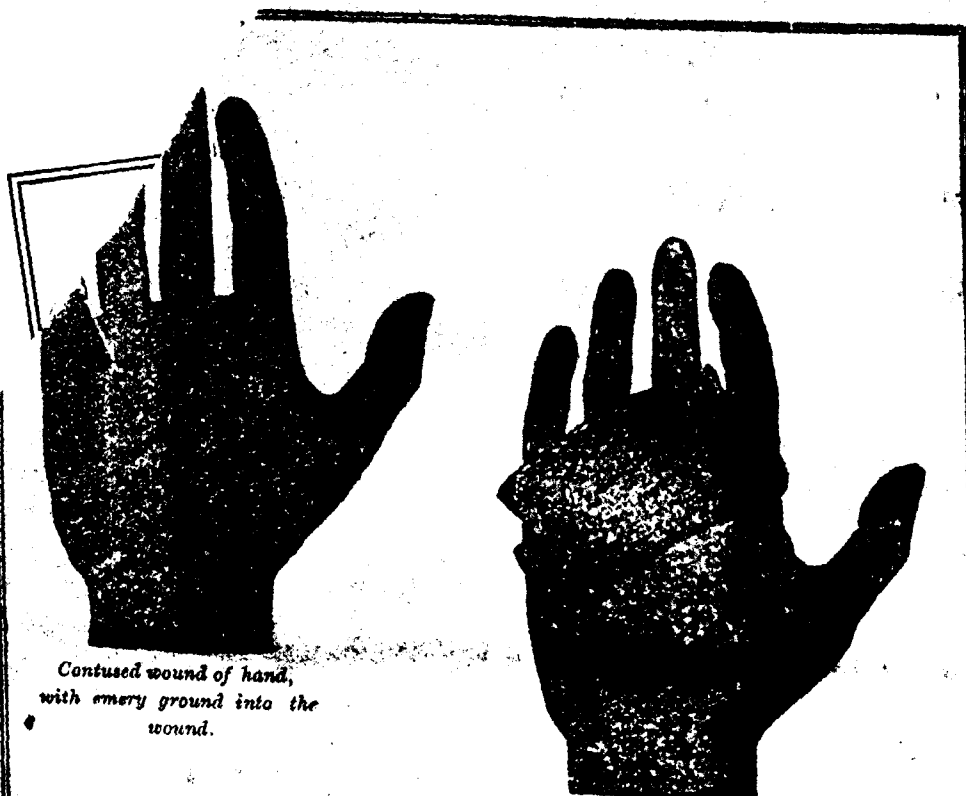
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